LECTURE NOTES

For Health Officers

Internal Medicine

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PREFACE

Internal medicine is a vast and complicated field that is based on strong scientific and clinical foundations. Moreover it is rapidly evolving and one needs periodic updating and catching up with the state of the art knowledge.

Providing a comprehensive review of internal medicine is not only difficult but almost impossible, as the field is vast and extensive. Despite this limitation, the authors have tried to provide a basic framework for working knowledge of Internal medicine. Essential topics are included as much as possible, and some chapters and topics are dealt extensively, such as Infectious diseases in general and Acute febrile illnesses, Tuberculosis, and HIV/AIDS in particular, as these are known to be the commonest causes of morbidity and mortality in developing countries, like ours.

Even though a number of individuals have contributed in the original document of this lecture note, as more than 3 years have elapsed, most of the topics are reviewed, and some topics are completely rewritten, to include new developments and the state of the art scientific knowledge.

This lecture note has been written primarily for Health officer students; however it can also be used by medical students and all other health science students who deal with patients, who have medical illnesses.

Getachew Tizazu

&

Tadesse Anteneh

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ABBREVIATIONS AND ACRONYMS

ABC – Airway, Breathing, and Circulation

ABG - Arterial blood gas

ACTH – Adrenocorticotrophic hormone

ADH – Antiduiretic hormone

AFB – Acid fast bacilli

AIDS – Acquired Immunodeficiency Syndrome

ALT/SGPT – Alanine aminotransferase

AMI – acute myocardial infarction

ANC – Antenatal care

APOC – African Programme for Onchocerciasis Control

ARDS – Adult respiratory distress syndrome

ARF – Acute rheumatic fever/acute renal failure

ARTs – Antiretroviral therapies

ASO titer – Antistreptolysin O titer

AST/SGOT - Aspartate aminotransferase

AV - Atrioventricular or arteriovenous

BCG – Bacille Calmette Guerin

BF – Blood film

BID – Twice a day

BLCM – Below left costal margin

BM – Bone marrow

BMI – Body mass index

BP - Blood pressure

BPH - Benign prostatic hypertrophy

BS – Blood sugar

BUN – Blood Urea Nitrogen

CAD – Coronary artery disease

CBC – Complete blood count

CHF - Congestive heart failure

CNS – Central nervous system

CPK - Creatine phosphokinase

CR – Creatinine

CRF - Chronic renal failure

CRH – Corticotrophic hormone

CSF – cerebrospinal fluid

CT – Computerized Tomogram

CTLs – Cytotoxic T Lymphocytes

CVD – Cerebrovascular diseases

CVS – Cardiovascular system

CXR – Chest x-ray

DAT – Direct agglutination test

DDI – Didanosine

D4T- Stavudin

DIC – Disseminated intravascular coagulopathy

Direct IF – direct Immunoflourescent

DKA – diabetic ketoacidosis

DM – diabetes mellitus

DNA- Deoxyribonucleic acid

DOTS – Directly Observed TB treatment Short course

DW - dextrose in water

EBV- Epstein-Barr virus

ECF – Extracellular fluid

ECG – Electrocardiogram

EFV – Efavirenz

ELISA – Enzyme linked immunosorbent assay

EPTB – extrapulmonary tuberculosis

ESR - Erythrocyte sedimentation rate

ESRD – End stage renal disease

ETB – Ethambutol

FBC – Full blood count

FBS – Fasting blood glucose

FSH – follicle stimulating hormone

GAS – Group A Streptococci

GDM - Gestational onset diabetes mellitus

GH – Growth hormone

GHRH – Growth hormone releasing hormone

GI - Gastrointestinal

GIT – Gastrointestinal tract

GnTH - Gonadotrophic hormone

GTT - glucose tolerance test

HAART – Highly active antiretroviral treatment

HAV - Hepatitis A virus

HBV – Hepatitis B virus

HCV – hepatitis C virus

HDL - high-density lipoprotein

Hgb – hemoglobin

HHV-8 – Human Herpes Virus-8

HIV –Human Immunodeficiency Virus

H_x – Clinical history

ICF – Intracellular fluid

ICU – Intensive care unit

IGT- Impaired glucose tolerance

IHD – ischemic heart disease

IM - Intramuscular

INH – Isoniazid

IV - intravenous

IVDU – Intravenous drug use

JHR – Jarisch Herxheimer reaction

JVP - Jugular venous pressure

KS – Kaposi Sarcoma

KUB –Kidney Ureter Bladder

LBRF – Louse borne relapsing fever

LDH - Lactate dehydrogenase

LDL - low-density lipoprotein

LH - Luetenizing hormone

LP – Lumbar puncture

LVH – left ventricular hypertrophy

MAC – Mycobacterium avium complex

MDR – Multidrug resistance

MODY 1, 2, 3 – Maturity onset diabetes of the young 1,2,3

MRI – Magnetic Resonant Imaging

MTCT – Mother to Child transmission

N/S – Normal saline

NCTs – Nerve conduction test

NK cells – Natural killer cells

NNN – Nichole MacNeal Novy medium

NSAIDs - Non-steroidal anti-inflammatory drugs

OEPA – Onchocerciasis Elimination Programme for Americas

OIs – Opportunistic infections

OMs – Opportunistic malignancies

P/E – Physical examination

P_aO_2 – partial pressure of arterial oxygen

PCP – Pneumocystis carinii pneumonia

PCR – Polymerase Chain Reaction

PFT – pulmonary function test

PLWHA – People living with HIV/AIDS

PML - Progressive multifocal leukoencephalopathy

PMTCT- prevention of Mother to Child transmission

PO – Per os (orally)

PPD – Purified protein derivative

PTB - pulmonary tuberculosis

PTU - Propylthiouracil

PZA - Pyrazinamide

QD – once a day

QID – four times a day

R/O – rule out

RBC - Red blood cells

RF – relapsing fever/Rheumatic fever

RHD – Rheumatic heart disease

RIF - Rifampicin

RNA – Ribonucleic acid

RPR – Rapid plasma reagin

S_1 - First heart sound

S_2 - Second heart sound

S_3 - third heart sound

S_4 – Fourth heart sound

SC - Subcutaneously

Stat - Once

STDs – Sexually transmitted diseases

TB – Tuberculosis

TBRF – Tick borne relapsing fever

TID – Three times a day

TLCP – TB leprosy control programme

TRH – Thyroid releasing hormone

U/S - Ultrasound

UTI – Urinary tract infection

VDRL – Venereal Disease Research Laboratory

WBC – white blood cells

WHO – World Health Organization

ZDV – Zudovudine

CMV – cytomegalovirus

UV-B – Ultraviolet B

UVA – Ultraviolet A

CHAPTER ONE
INFECTIOUS DISEASES

1. Introduction to infectious diseases

Generally infectious diseases result from bacteria, viruses, fungi, and parasites. Despite decades of dramatic progress in their treatment and prevention, infectious diseases remain a major cause of death and are responsible for worsening the living conditions of many millions of people around the world especially in the developing countries. Infections frequently challenge the clinician's diagnostic skill and must be considered in the differential diagnosis of syndromes affecting a multitude of organ systems. Infectious diseases often do not occur in isolated cases; rather they spread through a group exposed from a point source (e.g. a water supply contaminated with cholera) or from individual to individual (e.g. via respiratory droplets spreading tuberculosis). Many factors affect the likelihood of acquiring infections which include, host, environmental microbial factors.

Host and Environmental Factors

For any infectious process to occur, the parasite and the host must first encounter each other. Factors such as geography (e.g. altitude and malaria), environment (e.g. mosquito breeding site and malaria), disease vectors and host behavior (e.g. sexual behavior and sexually transmitted diseases) thus influence the likelihood of infection. Many **Host Factors** such as age, immunization, prior illness, nutritional status, pregnancy, coexisting illnesses and emotional status all have some impact on the risk of infection after exposure to a particular pathogen.

Medical care itself can increase the patient's risk of acquiring an infection. This can occur in several ways: through contact with the pathogens during hospitalization, through injections, surgical incisions, via mucosal surfaces by end tracheal tubes and bladder catheters, through the introduction of foreign bodies, through alteration of the natural flora with antibiotics, and through treatment with suppressive drugs such as steroids.

Microbial Factors

Infection involves complicated interaction of parasites and host and inevitably affects both. In most cases a pathogenic process consisting of several steps is required for the development of infections.

Since the competent host has a complex series of defense mechanisms in place to prevent infection, the successful parasite must utilize specific strategies at each of these steps. The specific strategies used by bacteria, viruses, and parasites have some similarities, but the details are unique not only for each class of organism but also for individual species within a class;

Invasion;

Microorganisms attached to mucosal surface use specific mechanisms to invade deeper structures. For example, meningococci and gonococci penetrate and traverse mucosal epithelial cells by transcytotic mechanism.

Tropism;

In order to infect a host successfully, many pathogens occupy highly specific place within the host and thus are tropic to a particular body site or cell type. For example, malaria sporozoites are rapidly cleared from the blood into the hepatocyts, where they undergo maturation and release into the circulation; trophozoites in turn can infect only the erythrocytes.

Microbial virulence strategies;

Microbes have developed a variety of strategies for escaping the immunity. For example, some pathogenic organisms elaborate toxins and enzymes that facilitate the invasion of the host and are often responsible for the disease state and many bacteria are encapsulated with polysaccharides that allow them to invade and deposit in the absence of specific antibodies.

Immune response:

Is a defense mechanism developed by the host for recognizing and responding to microorganisms. It is divided I to two major classes. Innate and Acquired Immunity.

Innate immunity (Natural Immunity):

Is first line of defense and serves to protect the host with out prior exposure to the infectious agent. This immune response is nonspecific and has no memory. Examples of Innate immunity include skin and mucous mebrane, phagocytoses by macrophages and nutrophils, complement system etc

Acquired (Adaptive) Immunity:

Is specific immune mechanism developed against a particular organism. It takes time to develop and it has long standing memory.

It has two major arms:

- **Cellular immunity**: comprising T- lymphocytes, NK cells
- **Humeral Immunity**: comprises of B-Lymphocytes and antibodies produced by plasma cells.

Laboratory diagnosis

The lab diagnosis of infections requires the demonstration, either

1. ***Direct*** microscopic visualization of pathogens in clinical material (e.g. Plasmodium species in blood films) or the growth of microorganisms in the laboratory (e.g. culture) or
2. ***Indirect*** (e.g. antibody / serology test for HIV), of viral, bacterial, mycotic, or parasitic agents in tissues, fluids, or excreta of the host.

Treatment;

Optimal therapy for infectious diseases requires a broad knowledge of medicine and careful clinical judgment. Life threatening infections such as bacterial meningitis and sepsis require urgent initiation of therapy often before a specific infective organism is identified. Antimicrobial agents must be chosen empirically and must be against the range of potential infectious agents consistent with the clinical condition. In contrast, good clinical judgment sometimes dictates withholding of antimicrobials in a self limited process or until a specific diagnosis is made. Certain infections (e.g. peritonitis, necrotizing fascitis, and abscess) require surgery as a primary means of cure; in these conditions, antibiotics play only as an adjunctive role.

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1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Intruducion to infectious diseases, pages 695-700.

2. Acute Febrile Illnesses

2.1. Malaria

***Learning Objective**:* At the end of this unit the student will be able to

1) *Define Malaria*
2) *List the etiologies of the different types of malarias*
3) *Describe the mode of transmission & the life cycle of malaria*
4) *Mention the epidemiology of malaria.*
5) *Explain the pathogenesis malaria*
6) *Identify the clinical features of the different malarial diseases*
7) *List the common complications of malaria.*
8) *Describe the most commonly used tests for the diagnosis of malaria*
9) *Make an accurate diagnosis of malaria*
10) *Treat malaria at the primary care level with appropriate drugs*
11) *Design appropriate methods of prevention & control of malaria*

Definition

Malaria is a protozoal disease transmitted to man by the bite of the female anopheles mosquitoes.

Etiology of Malaria

Malaria is caused by the protozoan genus plasmodium. Four species are known to cause disease in man

P. falciparum: also called malignant malaria
P. vivax : tertian malaria
P. ovale : tertian malaria
P. malariae : quartan malaria

N.B. Almost all deaths are caused by falciparum malaria

Epidemiology of malaria

- Malaria is one of the commonest infectious diseases of man having a global distribution with prevalence of 500 million people affected every year and about 2 million people die of malaria/year. 40 % of the world population living in tropical/subtropical climates are exposed to malaria. The prevalence of malaria is increasing because of the emergence of DDT resistant Anopheles mosquitoes, drug resistant plasmodia and global whether changes.

- Malaria is common in both low and high land areas and epidemics are commonly observed in the latter with elevations between 1600 to 2150 meters during the months between September and December. The disease is prevalent in 75% of the country with over 40 million people at risk.
- All human malarial parasites are found in Ethiopia, but ***P. falciparum and P. vivax*** are the commonest, accounting for 60% and 40% respectively. However *P. ovale* and P*. malariae* account for less than 1% of all cases,
- Endemicity of malaria is defined based on ***spleenic rates*** (palpable spleen) in children between 2 & 9 years. Depending on this, regions are classified in to 4 endemicity areas:-
    - ***Hypo endemic*** - Where < 10% children have enlarged spleen
    - ***Meso-endemic*** - Where 10-50% children have enlarged spleen
    - ***Hyper-endemic*** - Where 51-75% of children have enlarged spleen
    - ***Holo-endemic*** - Where > 75% of children have enlarged "

- In **Holo**- and H**yper** endemic areas there is an intense transmission of ***P. falciparum*** people can sustain more than one infectious mosquito bit per day – people are infected repeatedly in their lives. Is such places, morbidity and mortality are considerable during childhood. Immunity against disease is hard won and during adulthood most infections are asymptomatic. This frequent round-year transmission is termed **Stable transmission**.
- In **Hypo** and **Meso** endemic areas the transmission of malaria is low, erratic or focal, full protective immunity is not acquired and symptomatic disease may occur at all ages .This is termed as **Unstable transmission**.

Tablel-2.1-1 The basic characteristics of the two transmission types of malaria

	Stable	Unstable
Mosquito life	long	short
Mosquito bites	Frequent	Rare
Human immunity	High	Low
Epidemics	No (only with rainy Season & migration of non-immunes to the area	Yes
Eradication/ control	Difficult	Possible

Infant parasite rate is percentage of infants with positive blood smears for malaria. It is the most sensitive index of transmission of malaria to a locality.

Transmission

- Malaria is transmitted by the bite of the female anopheles mosquitoes or inoculation of blood. The female anopheles mosquitoes carry the plasmodium parasite and discharge into human body during feeding on a blood meal.

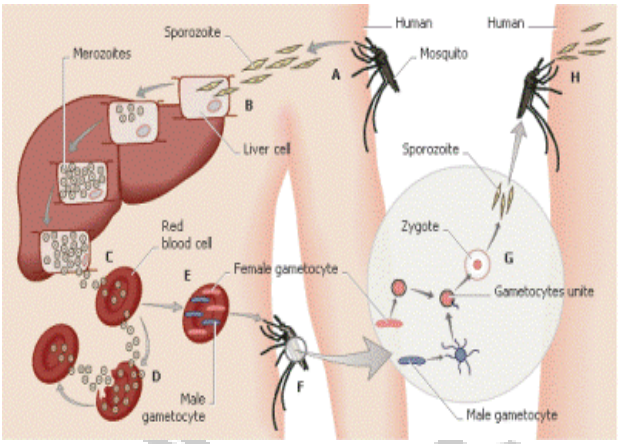
- Transmission of malaria requires high environmental temperature and collected water body, both of which are ideal conditions for breeding of mosquitoes. Therefore, transmission is common in lowlands during rainy season, especially with migration of non-immuned individuals to these areas. Rare cases of congenital transmission are known.

Life Cycle and Pathogenesis

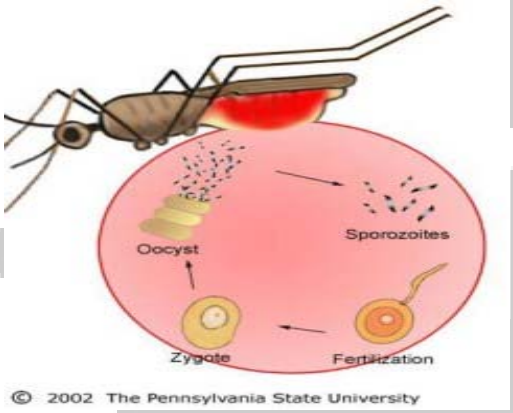
- The life cycle of plasmodium is divided into two, namely asexual and sexual cycles.
- Sexual cycle occurs inside the anopheles mosquitoes (definitive host)
- Asexual cycle occurs in human body which has two phases, namely
  - ***Liver phase (pre & exoerythrocytic phase) and***
  - ***Erythrocytic phase***

- Human infection begins with inoculation of plasmodium sporozoites by female anopheles mosquito during blood meal. The sporozoites are transported to the liver by the blood where they invade liver cells and undergo asexual reproduction. In this phase a single sporozoite produces thousands (10,000 – 30,000) of merozoites. The swollen liver cells rupture and discharge merozoites into the blood stream which then invade RBCs and multiply 6-20 fold every 48 to 72 hrs. When the parasites reach certain density in the blood, the symptomatic stage begins. In *P. vivax* and *P. ovale* some of these liver forms remain dormant (called hypnozoites) for months to years. These dormant forms (hypnozoites) are causes of relapses that characterize infection in these two species.
- After entry into the blood stream, merozoites invade red blood cells and become trophozoites. The trophozoites enlarge, develop pigment and then become amoeboid in shape and occupy most of the red cells consuming nearly all hemoglobin by the end of 48 hr of life in the RBC. It is now called schizont .Then multiple divisions give rise to several merozoites, which are released in to the blood stream when infected RBCs rupture and repeat the same cycle by invading other new RBC. This explains the anemia in malaria which is largely due to the destruction of RBC.
- During this process the infected RBC & sometimes uninfected ones are removed from the circulation by the spleen clearance function and contribute its share to the anemia. This immunologic function of the spleen causes enlargement of the organ.
- In P. falciparum infected RBC containing mature forms adhere to small blood vessels (called cytoadherence) and also with uninfected RBC forming rosettes (**called Rosetting**) , both of which result in sequestration of RBCs in vital organs like the brain and the heart and interfere with the micro circulation and metabolism and contribute to its severity. This makes detection of mature forms difficult, and only ring forms and gametocytes can be found on peripheral blood films. Sequestration is not a feature of other species of malaria and all stages of the parasite can be seen in the peripheral blood film.
- After a serious of asexual cycles some of the parasites develop in to morphologically distinct, long lived sexual forms (gametocytes) that can transmit malaria. During a blood meal gametocytes are taken by the female anopheles mosquito, the male and female gametocytes form zygotes, in the insect's midgut the zygotes mature in to ookinetes which then develop to oocystes and which divide to liberate several motile sporozoites.

Life Cycle of Parasite in Man



Life cycle of the parasite in the Mosquito



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Clinical features

The incubation period varies between 10-14 days in *P. vivax*, P. ovale, & P.falciparum, and 18days to six weeks in P. malariae.

Table I-2.1-2Types of plasmodium:and their clinical features

Type of malaria	Incubation period	Pattern of fever	Recurrence
A) Benign form:			
Plasmodium malaria	21 – 42 days	no fever for 2 days	no relapses
Pl. vivax / ovale (dormant hypnocytes may stay in liver and cause later relapse)	10 – 21 days	no fever for 1 day (both irregular at first)	relapses possible for up to 5 years
B) Malignant form: may lead to death within days, causes almost all of deaths due to malaria Pl. falciparum	7 – 20 days (Longer in 10 %)	Irregular rhythm of fever due to unsynchronized replication of parasites	no relapses

- Early symptoms are non- specific- malaise, fatigue, headache, muscle pain and abdominal discomfort followed by fever, nausea and vomiting is common.
- Classically malaria manifests in regular paroxysms of high grade fever, chills and rigor, occurring every 2 days in P. vivax and P.ovale, and every 3rd day in P. malariae, but irregularly in P.falciparum. Malarial febrile paroxysms (which are due to rupture of schizonts and release of pyrogens) typically have 3 stages
  - The “cold stage” the patient feels intensely cold & has shivering. This lasts for 30 minutes to 1hour.It is characterized by vasoconstriction of vessels & the temperature rises rapidly.
  - The” hot stage” The patient feels hot & uncomfortable, & become delirious. This stage lasts for 2-6 hours.
  - The “sweating stage” patient will have profuse sweating & become very much exhausted

Physical Findings

Uncomplicated infection has few physical findings except fever, malaise, and mild anemia, a palpable spleen and liver and mild jaundice e especially in children.

Severe and complicated Malaria

Is defined as life threatening malaria caused by P. falciparum, and the asexual form of the parasite demonstrated in a blood film.

Clinical Criteria for diagnosing of sever and complicated falciparum malaria in adults (the presence of one criteria already defines a complicated malaria)

- *Cerebral malaria: is a state of unarousable coma lasting for more than 30 minutes and other causes of coma ruled out.*
- *Change of level of consciousness less maked than unarousable coma*
- *Generalized tonic clonic sezure (> 2/day)*
- *Severe Normocytic anemia (Hgb < 5 g/dl)*
- *Acute renal failure (Oliguria of < 400 ml/24 h and/or creatinine > 3 mg/dl)*
- *Pulmonary edema or ARDS*
- *Hypoglycaemia (BS < 40 mg/dl) is multi factorial*
    - *The parasite consumes glucose*
    - *Catabolic state increases glucose demand of the host*
    - *Anorexia associated with the illness*
    - *Drugs like quinine can cause hypoglycaemia*
- *Metabolic acidociis (lactic acidosis) (pH < 7.25; plasma bicarbonate < 15 mmol/l)*
- *Circulatory collapse, shock ,septicaemia (" Algid Malaria "): systolic BP < 80 mmHg, core vs. skin temperature difference > 10°C)*
- *Spontaneous bleeding / Disseminated Intravascular coagulation (DIC)*
- *Hemoglobinuria*
- *Jaundice, bilirubine > 3 mg/dl*
- *Hyperparasitemia (>5 % of erythrocytes affected by plasmodium or > 100.000 plasmodium/µl)*
- *P. falciparum malaria in pregnant women is also considered as sever because it is associated with adverse out comes to the mother and the foetus*

These sever complications may occur singly, or, more commonly, in combination in the same patient

Who is at risk of developing severe malaria in high transmission areas ?

- Young Children
- Visitors from non Endemic areas of any age
- Pregnant women

Laboratory

Symptoms and signs of the disease are not specific to malaria, and resemble many types of febrile illnesses. Therefore confirmation of infection with laboratory investigations is essential.

1. Demonstration of the parasite by blood film (thin & thick) stained by Giemsa or Wright's stain

- ***Thin blood film*** is methanol fixed; you can see intact RBC with parasites inside it
  Advantage: species identification is simple; percentage of RBC parasitized can be estimated
- ***Thick blood film,*** not methanol fixed, RBC are lysed during staining, parasites are seen free from RBC
  Advantage: concentrates the parasite 20-40 times, this helps to determine parasite concentration.

NOTE: A single blood film examination doesn't rule out malaria, and it should be repeatedly done possibly during febrile episodes. However, studies have shown that BF can be negative in small percentage of patients with malarias

Other Lab Tests

- Hemoglobin- anemia can be detected
- Blood glucose
- Peripheral morphology- Normocytic normochromic anemia - Low or normal WBC
- LP and CSF analysis (when indicated to R/O Meningitis)
- BUN/ Cr, SGOT , SGPT , Serum electrolytes etc

Treatment

Depends on the type of malaria and the severity of the diseases

A. Benign forms of malaria (Plasmodium malariae, vivax, ovale):

Chloroquine is effective

Dose: Initial dose is 600 mg PO followed by 300mg after 6, 24 and 48 h subsequently.

N.B Cloroquine is no effect on the exoerythrocytic liver form (= reservoir). To protect from later recurrences, chloroquine therapy should be followed by:-

Primaquine: (dose: 15 mg/day over 2 weeks), which is effective against liver forms and gametocytes.

B. Treatment of P.Falciparum malaria

- The high treatment failure rates of chloroquine for the treatment of uncomplicated P.falciparum malaria as documented through a nationwide study conducted in 1997/98 in Ethiopia, led to a treatment policy change that recommends the use of Sulfadoxine-Pyrimethamine as first line drug for the treatment of uncomplicated falciparum malaria and chloroquine for the treatment of vivax malaria.
- In subsequent years, however, unpublished reports from isolated studies indicated higher treatment failure rates. Accordingly, a nationwide study on the therapeutic efficacy of Sulfadoxine-Pyrimethamine for the treatment of uncomplicated falciparum malaria was conducted in 11 sentinel sites from October – December 2003. Results obtained from the study showed a mean treatment failure rate of 35.9% on the 14-days follow-up and 71.8% on the 28-days follow-up.
- This level of treatment failure rate is much higher than the cut-off point recommended by WHO for a treatment policy change. *In-vivo* therapeutic efficacy and safety baseline study on artemether-lumefantrine was also conducted in 4 sites by enrolling 213 subjects and after a follow-up period of 14 days, no treatment failure cases and drug side effects were reported

i) Treatment of uncomplicated falciparum malaria**:** oral drugs are used can be used

In most tropical countries since resistance to chloroquine and Sulfadoxine-pyrimethamine is well documented other drugs are recommended.

a) **Aritemisinin and its derivatives were developed originally in China, have proved to be highly effective in adults and children.**

There are different preparations like, Artesunate PO, or IV), Artemether (PO, IM)

- **Artemether-Lumefantrine: (Coartem 20/120):** is most widely used in Ethiopia. Tablet containing 20 mg Artemether plus 120 mg Lumefantrine in a fixed dose combination.

Adult Dosage: < 35 kg: 3 tabs PO BID for 3 days

> 35 Kg: 4 tabs PO BID for 3 days

Side effects: Dizziness and fatigue, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthralgia, headache and rash.

Contra-indications:

- As malaria prophylaxis either alone or in combination.
- Persons with a previous history of reaction after using the drug
- Pregnant women, mothers with infants less than three months of age and Infants less than 5 kg

b) Quinine:

Adult dose : 600 mg PO TID for 5 – 7 days alone or in combination with + Tetracycline 500 mg PO QID or Doxycycline 100mg PO /day for the same period

Side effects:

- **Cinchonism:** Tinnitus, hearing loss, dizziness, tremor, nausea, resteleness, blurring
- **Hypogycemia** : is the commonest adverse effect

c) Mefloquine : Structurally ressembles Quinine. It is effective against all malarial specious including multi-drug resistant P.falciparum. However some resistance strains of P.falciparum for Mefloquine are reported in some tropical countries.

Dose: 15mg/kg followed by second dose of 10mg/kg after 8-12 hr

Side Effects: Nausea, abdominal cramp, vertigo, insomnia, sometimes acute psychosis and convulsion

d) Sulfadoxine-pyrimethamine (oral) e.g. Fansidar-3 tablets stat as a single dose. (1 tablet = 500mg sulfadoxine + 25 mg pyrimethamine). Contraindicated in children less than one year. Due to high prevalence of resistance to this combination, it is not recommended for treatment of P.faciparum in most tropical countries including Ethiopia.

–5 days (e.g 4 mg /kg for 3 days) in combination with Mefloquine 25 mg/kg

Treatment of Severe and complicated falciparum malaria:

NB: Patients should be admitted and treated in a Hospital setting

A) ***Drug Treatment:***

i) Quinine: is drug of choice for severe and complicated malaria.

Dosage and Adminstration:

Where IV administration of quinine is possible

Loading dose: Quinine 20 mg salt/kg of body weight by infusion over 4 hours, in 5 % dextrose in saline (5-10 ml/kg of body weight depending on the patient's overall fluid balance).

Maintenance does: Twelve hours after the start of the loading dose, give quinine 10 mg salt/kg of body weight in dextrose saline over 4 hours. Repeat the same dose of quinine (i.e. 10 mg salt/kg) every 8 hours until the patient can take oral medication.

Wherever IV administration of quinine is not possible.

Quinine dihydrochloride 20 mg salt per kg loading dose intramuscularly divided in to two sites, anterior thigh). Then quinine dihydrochloride 10 mg salt per kg IM every 8 hours until patient can swallow.

ii) Artesunate injection (if available) : 2.4 mg/kg IV or IM stat followed by 1.2 mg/kg at 12 and 24 hrs and then daily.

B) ***Supportive treatment:***

- Bring down fever (cold sponges, paracetamol)
- Administer glucose IV or PO to prevent hypoglycaemia and encourage early PO intake of food
- Ensure adequate fluid intake, check input and output and control water and electrolyte balance (beware of pulmonary edema due to fluid overload).
- Consider transfusion in severe falciparum malaria with high parasitemia (> 20% of erythrocytes affected by plasmodium)
- Check renal function tests and blood sugar (beware of hypoglycemia).
- For comatose or unconscious patients proper nursing care is mandatory
  - Position the patient on his/her sides; turn every 2 hours to avoid bed sores.
  - Catheterize the bladder, monitor input-output.
  - Avoid fluid overload
  - Monitor blood glucose regularly
  - Ensure adequate nutrition

Chronic Complications of Malaria

Tropical Splenomegaly Syndrome (Hyperreactive malarial Splenomegaly)

It is a syndrome resulting from an abnormal immunologic response to repeated infection. Is seen is some residents of malaria endemic area in tropical Africa and Asia

It is characterized by

- Huge spleen (> 10 cm BLLCM) with or with out hepatomegaly
- Hyperspleenism (anaemia, pancytopenia)
- Marked elevation of serum **IgM** and anti malarial antibody
- Hepatic Sinusoidal lymphocytes
- Peripheral B-Cell lymphocytosis

Clinical Feature:

- Abdominal mass or dragging sensation in the left upper quadrant and sometimes abdominal pan
- Anaemia and sometimes Pancytopenia → susceptibility to Infection
- The parasite may not be detected in peripheral blood film

Treatment

- Antimalarial prophylaxis for a long time, usually for the duration of malaria exposure.
- Drugs commonly used are chloroquine or mefloquine.
- The enlarged spleen and liver usually regress over a period of months with effective Antimalarial prophylaxis.
- Splenectomy is only indicated for those with failure of antimalarial prophylaxis at least given for 6months.

Prevention of Malaria

A. General measures

Mechanical Barriers/Methods

- Draining water collections and swampy areas
- Use of chemical impregnated mosquito nets around beds
- Wire mesh across windows
- Staying indoors at night
- Use of long sleeved shirts and long trousers

Insecticides or Chemicals

- Use insecticide spray aerosols (permethrin, deltamethrin and chlorinated hydrocarbons)
- Application of insect repellents to exposed skin (e.g. diethyltoluamide)
- DDT sprayed in the interior of houses is effective in killing the adult mosquito for many months.

B. Drug prophylaxis

It is indicated for

- Pregnant women in endemic areas because of their increased risk of severe malaria
- Children between 3 months and 4 years in endemic area (born to non-immune mother)

- Travelers to malarious areas → they should start taking drugs 1 week before traveling to these areas & for 4 weeks after the individual left the endemic area.

Drugs available for prophylaxis

In Areas where there is chloroquine resistant P. falciparum

- Mefloquine 250mg/week orally, effective against multi drug resistant p. falciparum, safe during pregnancy
- Doxycycline 100mg daily orally , not used for children < 8 years& during pregnancy
- Maloprim (Pyrimethamine+ dapson) 1 tab orally/wk
- Chloroquine+ proguanil combination alternative to mefloquine and doxycycline.

In areas where there is for chloroquine sensitive P.falciparum and other" benign" malarias:

- Chloroquine 2 tabs of 150 mg tablet orally every week
- Chloroquine+ proguanil combination can be used as an alternative

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Salmonellosis, pages 1218-1232.
2) Gordon c cook and Alimuddin Zumla, Manson's Tropical Diseases, 21st edition, 2003, pages 937 – 949.
3) Management of severe and complicated malaria in Ethipoa , Federal MOH , 2005

2.2 Typhoid (Enteric) Fever

Learning Objective: At the end of this unit the student will be able to

1. *Define Typhoid fever*
2. *List the etiologies of typhoid fever*
3. *Describe the epidemiology of typhoid fever .*
4. *Explain the pathogenesis typhoid fever*
5. *Describe the clinical features of typhoid fever*
6. *List the common complications typhoid fever .*
7. *Describe the most commonly used tests for the diagnosis of typhoid fever*
8. *Make an accurate diagnosis of typhoid fever*
9. *Treat typhoid fever with appropriate antibiotics*
10. *Design appropriate methods of prevention and control of typhoid fever*

Definition: Typhoid fever is a systemic infection characterized by fever and abdominal pain caused by dissemination of Salmonella typhi and occasionally by S. paratyphi A and B and S.typhimarium, all of which are non capsulated, gram negative motile bacteria.

Epidemiology

- Human beings are the only hosts for S. typhi and S.paratyphi. Thus enteric fever is transmitted only thorough close contact with acutely infected individuals or chronic carriers through ingestion of contaminated food or water.
- Chronic carriers are the source of infection harboring the organisms in their gall bladder (especially in the presence of gall stones) and rarely at other sites. It affects people of all ages and both sexes. Enteric fever is endemic in most developing countries.
- Currently the disease is observed at a great frequency in AIDS patients than the general population.

Pathogenesis

Following ingestion of the organism in contaminated food or drink, Salmonella typhi passes the gastric barrier and reach the upper small intestine where the bacilli invade the intestinal epithelium and they are engulfed by phagosoms which reside in the Peyer's patches. The bacilli multiply and enter the blood stream and cause transient bacteremia. At this stage the

Salmonellae disseminate throughout the body in macrophages via lymphatic and colonize reticuloendothilial tissue (liver, spleen, lymph nodes, and bone marrow). Patients have relatively fewer or no signs and symptoms during this initial incubation period. Signs and symptoms, including fever and abdominal pain result when a critical number of bacteria have replicated. During weeks after initial colonization, further inflammation of the Peyer's patches may result enlargement and necrosis which may result intestinal hemorrhage and perforation. Infection may become persistent and invade the gall bladder. The clinical phase of the disease depends on host defense and bacterial multiplication.

Clinical Manifestation

The incubation period varies from 3-60 days. The manifestation is dependent on inoculum size, state of host defense and the duration of the disease. The Severity of the illness may range from mild, brief illness to acute, severe disease with central nervous system involvement and death.

First week

- Fever is high grade, with a daily increase in a step-ladder pattern for the 1st one week and then becomes persistent.
- Headache , malaise , Abdominal pain
- Initially diarrhea or loss stole followed by constipation in adults, diarrhea is dominate feature in children
- Relative bradycardia
- Splenomegally Hepatomegaly
- "Rose spots" not commonly seen in black patients. In whites it appears as small, pale red, blanching macules commonly over chest & abdomen, lasting for 2-3 days.
- Epistaxis

Second week

- Fever becomes continuous
- The patient becomes very ill and withdrawn confused, delirious and sometimes may be even comatose

Third Week

- The patient goes to a pattern of “typhoidal state" characterized by extreme toxemia, disorientation, and “pea-soup” diarrhea and sometimes may be complicated by intestinal perforation and hemorrhage.

Fourth Week

- Fever starts to decrease and the patient may defervesce with resolution of symptoms. At this point patient may lose weight.
- Relapse may occur in 10% of cases.

Complications of Typhoid fever

- Gastrointestinal perforation and hemorrhage: are late complications that may occur in the 3rd or 4th week. May develop despite clinical improvement. These complications are life threatening and need immediate medical and surgical interventions
- Other Less common complications
  - Hepatitis
  - Meningitis .
  - Arthritis, osteomyelitis
  - Parotitis and orchitis
  - Nephritis
  - Myocarditis
  - Bronchitis and pneumonia

N.B these complications can be prevented by prompt diagnosis and treatment

Chronic Carriers

- Approximately 1- 5 % of patient with Enteric fever become asymptomatic chronic carriers
- They shed *S.typhi* in either urine or stool for > 1 year
- Incidence of Chronic carriage is high in women and among patients with biliary abnormality (e.g. gall stone, carcinoma of gall bladder) and other GI malignancies.

Diagnosis

Can be suggested by the presence of

- Persistent fever
- Relative bradycardia, which was found to occur in 86% of Ethiopians.
- Rose spots, which occurs in 70% of whites and 20% of Ethiopians.

- Leucopenia

But definitive diagnosis of the disease requires laboratory tests.

1. **Isolation of the organism** by blood, stool or urine culture is diagnostic.
    - The yield of recovery of the organism differs depending on the specimen cultured and the duration of clinical disease;
    - **Blood culture** -mostly (up to 90%) patients have positive culture in the 1st week, and only 50% by the 3rd week. The yield is much lower if patient has taken antibiotics prior to the test.
    - **Stool culture** is negative in the first week and becomes positive in 75% of patients in the 3rd week. Urine culture parallels stool culture.

Widal test for O and H antigens

- The O (somatic) antigen shows active infection whereas the H (flagellar) antigen could be indicative of past infection or immunization for typhoid.
- Widal test has certain limitations, and to make a diagnosis of current infection a 4X (fold) rise in titer on paired sera taken during the acute and convalescence phases is necessary.

Limitations of Widal test

- It is non specific and a positive test could be due to
    - Infection by other salmonellae (as the antigen used for the test is also shared by other salmonellae)
    - Recent vaccination for typhoid
    - Past typhoid (already treated)
- The demonstration of 4- fold rise in titer on paired sera is not useful for the treatment of acute cases, as this requires waiting for the convalescence phase of the disease and at this stage if the patient is lucky recovery will occur.

Treatment

Antibiotic therapy is curative. These drugs can be given either orally or intravenous, depending on patient condition (able to take orally or not), severity of the disease. One should note that fever may persist for 4-6 days despite effective antibiotic treatment

Oral drugs

First Line

Nowadays 4-amino quinolones are the drugs of choice because of their effectiveness on multidrug resistant typhoid, and low relapse and carrier rates. Ciprofloxacin, norfloxacin, ofloxacin, and pefloxacin are all equally effective.

- **Ciprofoxacin:** 500mg PO BID for 10 days
- **Ceftriaxone** 1-2 gm IM or IV for 10 -14 days

4- amino quinolones are not recommended for use in children and pregnant women because of their observed potential damaging effect on cartilage of the growing animals. However, in severe infections especially by MDR strains, we have to outweigh the benefits and the potential risks.

Alternative

- **Azithromycine** 1 gm PO daily for 5 days
- **Chloramphenicol** 500 mg Po QID for 14 days
- **Norfloxacin** 400mg twice daily for 10 days

Chloramphenicol is very cheap and also quite effective with initial doses of 3 - 4 g/d for adults, with clinical response observed in 24 - 48hrs after initiation. Dose should be reduced to 2g/d when fever starts to decrease (usually after 5 - 6 days), and continued to complete 2 weeks treatment.

Intravenous drugs are recommended for critically sick patients who are admiited or for patients who are unable to take oral drugs

- Ceftriaxone 2-4gm once a day for 3 days and then 1- 2gm IV/IM for a total of 10- 14 days.
- Intravenous Chloramphenical 1gm IV QID for 2-3 days and then start PO medication as soon as the patient can take oral medication. This is a drug of choice for patients that need parenteral therapy especially in Ethiopia (mainly for cost reason).

Problems of antibiotic treatment

- Multidrug resistant (MDR) *S.typhi* is reported in different parts of the world, especially Indian subcontinent and Southeast Asia. Hence if resistance is suspected in an area, the preferred treatment would be with quinolones, azithromycin or third generation cephalosporins

- Early use of antibiotics is associated with high rate of relapse (up to 20%) as compared to untreated cases (where the relapse rate is 5 - 10%). This is due to inhibition of adequate development of immune response by early therapy.
- **Eradication of chronic carrier state** requires prolonged treatment with
  - Ciprofloxacin for 4 weeks is effective and much better than the other drugs
  - Ampicillin or Amoxicillin 100mg/kg/d taken with Probenecid 30mg/kg/day for 6 weeks.
  - Co-trimexazole (160/800mg twice a day) plus Rifampicin 600mg orally/d for 6 weeks..

N.B. Drug treatment does not eradicate infection in 40% of the chronic carriers. Hence surgical resection of the gall bladder may sometimes be necessary.

Prevention and control

- Improve environmental sanitation
- Identification and treatment of Chronic carriers
- Avoid food handling by chronic carriers
- Vaccination for travelers to endemic areas
  - Live oral vaccine (TY21a) 3 doses can be given to those over 6 years. Protective for several years
  - Purified Vi polysaccharide vaccine given in a single dose to those over 2 years and HIV positives, is as effective as live vaccine.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Salmonellosis, pages 897 - 902 .
2) Gordon c cook and Alimuddin Zumla, Manson's Tropical Diseases, 21st edition, 2003, pages 937 – 949.

2.3 Relapsing Fever

Learning Objective: At the end of this unit the student will be able to

1. *Define relapsing fever*
2. *List the etiologies of the two major types of relapsing fever*
3. *Describe the mode of transmission relapsing fever*
4. *Mention the epidemiology of relapsing fever*
5. *Describe the pathophysiology of relapsing fever*
6. *Identify the different features of the two types of borrelia and their clinical manifestations*
7. *List the complications of relapsing fever*
8. *Describe the most commonly used tests for the diagnosis of relapsing fever*
9. *Make an accurate diagnosis of relapsing fever*
10. *Manage relapsing fever at the primary care level with appropriate drugs*
11. *Design appropriate methods of prevention and control of relapsing fever*

Definition

Relapsing fever is an acute febrile illness caused by Borrelia species, presenting with recurrence of characteristic febrile periods lasting for days alternating with afebrile periods. Relapsing fever describes two distinct diseases:

- Louse borne (Endemic) relapsing fever (LBRF):- transmitted by body louse Pediculus humanis var corporis
- Tick borne (Epidemic) relapsing fever (TBRF)- transmitted by tick (Ornithodoros)

Etiology

Relapsing fever is caused by Borrelia species, which are spirochetal gram negative helical bacteria.

- *B. recurrentis* is the only species that cause LBRF
- *B. duttoni* is the commonest causes of TBRF in sub-Saharan Africa.

Borrelia demonstrates remarkable antigenic variation and strain heterogeneity which help the parasite to escape the immune response of the host and result in recurrence of febrile episodes.

Transmission:

LBRF: Body lice become infected by *B. recurrentis* while *feeding* on spirochetemic human blood, the only reservoir of infection. Humans acquire infection when infected body lice are crushed and their fluids contaminate mucous membrane or breaks in the skin (such as abrasions caused by scratching of pruritic louse bites)

LBRF is now an important disease only in the northeastern Africa, specially the highlands of Ethiopia where an estimated 10,000 case occur annually. In Ethiopia the diseases affects mostly homeless men living crowded together in very unhygienic circumstances especially during rainy seasons. Some of the risk factors for LBRF are over crowding like in military camps, civilian population disrupted by war and other disasters.

TBRF: Rodents are the primary hosts and vector ticks become infected when they feed spirochetemic rodents. Ticks transmit the borreliae vertically over several generations. TBRF is most highly endemic in sub-Saharan Africa but also is found in Mediterranean and Middle eastern countries.

Pathophysiology

In humans, borreliae after entering the body multiply in the blood and circulate in great number during febrile periods. They are also found in the spleen, liver, central nervous system, bone marrow, and may be sequestered in these organs during periods of remission. Severity is related to spirocheatal density in blood but systemic manifestations are related to release of various cytokines.

The disease is characterized by sub capsular and parenchymal hemorrhage with infarcts of spleen, liver, heart and brain is seen. Thus, patients will have enlarged spleen and liver with variable edema and swelling of brain, lung and kidneys. Relapsing fever in pregnancy can result abortion, still birth and fatal neonatal infection

Death from TBRF is rare. In contrast fatality rate of LBRF may reach up to 20 % during out beaks mainly among malnourished and stressed population.

Clinical Features

- The manifestation of both LBRF and TBRF are similar.
- Incubation period is 7 days (ranging from 2-18 days).

- The onset is sudden with high grade irregular fever, headache, chills, myalgias, arthralgias, and insomnia.
- Patient will be withdrawn, disinterested to food and other stimuli and thirsty. Patient will have delirium associated with high grade fever, tachycardia and dry tongue, injected conjunctiva and photophobia
- Summation gallop , occasionally resulting from myocardial involvement
- Upper abdominal tenderness with hepatosplenomegally,
- Scattered petechiae over the trunk, extremities and mucous membrane in 1/3 LBRF and fewer TBRF
- Symptoms and signs of meningial irritation may be seen in some patients.
- Icteric sclera may be found in late stage of the disease.

Complications:-

Life threatening complications are unusual in otherwise healthy persons if the disease is diagnosed and treated early. Complications are common in late disease in untreated patients.

- Epistaxis, blood streaked sputum other bleeding tendencies
- Neurologic manifestations like iridocyclitis, meningitis, coma, isolated cranial nerve palsies,
- Pneumonitis,
- Myocarditis
- Spleenic rupture of spleen etc. .

Without treatment, symptoms intensify over 2-7 days period and subside with spontaneous crisis during which borrelia disappear from the circulation. Such cycles of febrile periods alternating with afebrile periods may recur several times.

Table I-2.3-1 Basic characteristics of the two types of borreliae

	LBRF	**TBRF**
Causes	B. recurrent is	B. duttoni + many others(all zoonotic
Parasite in the vector	Found in endolymph of lice	Found in all tissues, including salivary glands & ovaries

Transmission	Contamination of mucous membrane or breaks or abrasions on the skin by body fluids of lice, released during crushing - Not transmitted by the bite of lice or inoculation of louse feces	By bite of tick during blood meal (organisms in the saliva & coaxal fluid of borrelia)
Vertical transmission (Tran Ovarian)	No	Yes
Distribution	East Africa-Ethiopia	Sub-Saharan Africa, Mediterranean littoral, middle east, Russia, India, China, USA
Occurrence	Epidemics are frequent in homeless people living in unhygienic crowded condition	Sporadic or in small often familial clusters
Vector longevity	Short life span	Lives over 10 Yrs
Jarisch – Herxheimer Reaction	More sever	Less sever
Eradication	Easy	Difficult because of: - the night biting habit & painless nature of the bite of ticks - vertical transmission/trans-ovarian/ - long life span.

Diagnosis

- Diagnosis of relapsing fever is made based on demonstration of the organisms in blood, bone marrow, CSF etc

Blood Film:

- Giemsa or Wright stained peripheral blood smear is the most commonly done laboratory test in Ethiopia, and an ideal test in the resource limited setting.
- Spiral organisms can be demonstrated on peripheral blood taken during febrile period preceding the crisis. This is positive in more than 70% of LBRF and in lower percentage of patients with TBRF.

Other Tests

- Dark field microscopy of unstained blood/CSF
- Serologic tests

Treatment

Relapsing fever is treated with antibiotics. In LBRF single dose of erythromycin, tetracycline, doxycycline or chloramphenical, produces rapid clearance of borrelia from the blood & remission of symptoms. TBRF is less sensitive to these antibiotics and requires a 7 days course of treatment.

Adult Dosage

Medication	**LBRF (single dose)**	**TBRF (7 day schedule)**
Oral		
• Erythromycin	500mg	500mg every 6 hrs
• Tetracycline	500mg	500mg every 6 hrs
• Doxycycline	100mg	100mg every 12 hrs
• Chloramphenicol	500mg	500mg every 6 hrs
Parenteral		
Penicillin G (procaine)	600,000 I.M stat	600,000 IM daily

Delousing of patients with Relapsing fever is important to prevent transmission and recurrence

Jarisch- Herxheimer Reaction (JHR)

- Rapidly acting antibiotics regularly precipitate JHR within 1- 4 hrs of 1st dose
- More sever in patients with LBRF than TBRF
- It is more sever when high numbers of spirochetes are circulating in the blood
- Jarisch- Herxheimer Reaction has three phases

Chill phase:- lasts for 10- 30 minutes

- Rigor, hyperventilation, high cardiac output,
- High body Temperature (> or = 41 C^{o}) accompanied by , agitation , confusion

Flush phase:

- Fall in body temperature, drenching sweating, Potential dangerous fall in Systemic blood pressure (as peripheral vascular resistance falls)

- Clinical and ECG evidence of myocarditis may be seen , S_3 gallop and prolonged QT interval
- Vitals signs must be monitored closely during this time which usually lasts for <or = 8 hrs

Recovery (Deferverescence) phase

- Vital signs slowly come to normal
- The Patients is exhausted ,

Treatment of JHR

- Close monitoring of vital signs
- Care full fluid management
- Control high body Temperature
- Short term digoxin I.V administration in patients with evidence of myocardial dysfunction

Prevention and Control of Relapsing Fever

- Avoiding over crowding
- Apply hygienic practices that reduce the number of body lice (washing clothes)
- Elimination of ticks
- Health education
- Early case detection and treatment of infected persons and close contacts
- In out breaks of LBRF, empirical single dose treatment with doxycycline
- Eradication of Rodents to control TBRF: (Rodenticides)

References

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Relapsing fever, pages 991-994.
2) Gordon c cook and Alimuddin Zumla, Manson's Tropical Diseases, 21st edition, 2003, pages 937 – 949.

*2.4 Rickettisial diseases: (*Epidemic and Endemic Typhus)

Learning Objective: At the end of this unit the student will be able to

1. *Define rickettsial diseases with Special Emphasis on Epidemic and Endemic Typhus*
2. *Classify rickettsial diseases*
3. *List the etiologies of the different types of rickettsial diseases*
4. *Describe the mode of transmission rickettsial diseases*
5. *Explain the epidemiology of rickettsial diseases*
6. *Describe the pathophysiology of rickettsial diseases*
7. *Identify the clinical manifestations of the different types of rickettsial diseases*
8. *List the complications of rickettsial diseases*
9. *Describe the most commonly used tests for the diagnosis of rickettsial diseases*
10. *Make an accurate diagnosis of rickettsial diseases*
11. *Refer complicated cases of rickettsial diseases to hospitals for better management*
12. *Design appropriate methods of prevention and control of rickettsial diseases*

Definition:

Rickettisiae are small intracellular bacteria that are spread to man by arthropod vectors, namely human body lice, fleas, ticks & larval mites. The organisms inhabit the gastrointestinal tract of these arthropods & spread to human host by the direct bite of the vector or the inoculation of the organism contained in the feces of the vector by bite induced body itching. These infections are characterized by persistence in the body, widespread vasculitis (invading endothelial cells of small blood vessels) & multi-system involvement. Except in louse borne typhus humans are accidental hosts in most rickettisial diseases.

Classification

Rickettsial diseases are classified into five general groups

- Tick and mite borne spotted fever group
- Flea and louse borne typhus group
- Chigger borne scrub typhus
- Ehrlichiosis
- Q-fever

***Etiology and Epidemiology of Epidemic and Endemic Typhus* :**

Epidemic Typhus (Louse born): is caused by ***R.prowazekii*** and transmitted by human body louse (Pediculus humanus corporis). Lice acquire the rickettsia while ingesting a blood meal from an infected patient, the rickettsia multiply in the midgut epithelial cells of the louse and are excreted via louse faeces. The infected louse defecates during a blood meal and the patient autoinoculates the organisms by scratching. It is commonly associated with poverty, cold weather, war and natural disasters. The disease is prevalent in mountainous areas of Africa, South America, and Asia.

Endemic Typhus (Flea born) / Murine Typhus: is cause by ***R. thyphi*** which is transmitted by fleas. *R.typhi* is maintained in mammalian host/flea cycles, with rats. Fleas acquire R.thyphi from rikettsemic rats and carry the organism throughout the rest of their life span. . Humans and rats are infected when rickettsia –laden fleas are scratched in to pruritic bite lesions.

Pathophysiology

In man rickettsia multiply in the endothelial cells of capillaries causing lesions in the skin, brain, lung, heart, kidneys and skeletal muscles. Endothelial proliferation coupled with peri-vascular reaction causes thromboses and small hemorrhages. However, tissue and organ injury is commonly due to increased vascular permeability with resulting edema, hypovolemia and organ ischemia. This leads to multi-system involvement with complications such as non-cardiogenic pulmonary edema, cardiac dysrhythemia, encephalitis, renal and hepatic failure and bleeding.

Clinical Features

Signs and symptoms:

- Incubation period of 1 week
- Abrupt onset of illness with prostration, severe headache and rapidly rising fever of 38.8 to 40.0 °C
- Cough s seen in 70 % of patients , myalgia may also occur which may be severe
- Rash, begins on upper trunk around 5th day and then becomes generalized, involving the entire body except face, palms and soles; at first, rash is macular, becoming maculopapular, petechial and confluent without treatment, although in black people, rash may be absent (*spotless epidemic typhus*)
- Photophobia, with conjunctival injection and eye pain; frequent

- Tongue may be dry, brown, furred
- The signs of central nervous system involvement, commonly as meningo-encephalitis, appear towards the end of the 1st week progressing to seizure and coma.

Brill-Zinsser disease *(recrudescent typhus)*: This is a mild form of epidemic typhus caused by reactivation of dormant *R. prowazekii* in the body (in the lymph nodes) as a result of immunosuppression or old age. Occurs after several years of acute infection. The manifestation of the disease is similar to acute epidemic typhus but milder. The organisms may infect other people in the presence of vectors (body lice).

Endemic typhus (Flea borne typhus)

- Epidemic typhus (also known as murine typhus) is a relatively milder.
- The incubation period is 1 - 3 weeks and followed by sudden onset of fever, rigors, frontal headache, pain in the back and limbs, constipation and cough (due to bronchitis).
- The fever becomes constant after the third day and associated with conjunctivitis and orbital pain.
- Rash appears on the fifth day initially as blanching macules at the anterior axillary folds, which subsequently spread to involve other parts of the body (sparing the face & the neck) and become purpuric.
- During the second week symptoms worsen and additional manifestations, such as sore lips, dry brown tremulous tongue, feeble pulse, enlarged spleen & delirium appear.

Complications of Endemic and Epidemic Typhus

- Skin necrosis, gangrene of digits,
- Venous thrombosis
- Interstitial pneumonia in severe cases
- Myocarditis
- Oliguric renal failure
- Parotitis

Diagnosis of rickettsial diseases is based on

History, clinical course of the disease and epidemiologic of the disease may give a clue for diagnosis.

Laboratory investigations*;*

Serologic tests:

- Indirect fluorescent antibody test
- **Weil-Felix agglutination test**: This is widely used by many of the hospitals and the private clinics in this country, is not specific or sensitive.

Isolation of the organism by inoculation into laboratory animals is possible, it is time consuming and technically demanding.

Treatment of rickettsial diseases

Endemic Typhus

- Doxycycline 100mg bid PO for 7-15 days
- Chloramphenicol 500mg QID PO for7-15 days

Epidemic typhus

- Doxycycline 200mg as single dose PO until the patient is afebrile for 24 hours.
- **Delousing louse borne typhus**

Supportive Therapy

- Attention to fluid balance, prevention of bed sores,
- Treat agitation with diazepam
- Steroid treatment (prednisolone 20 mg daily for adults) in severe cases

Prognosis: Untreated disease is fatal in 7 to 40 % of cases, depending on condition of host. In untreated survivors, renal insufficiency, multiorgan involvement and neurologic manifestations (12 %) are common. However, endemic typhus has better prognosis with a mortality of only 1 – 2%. Serious neurological, renal and other complications are unusual.

Prevention

For flea borne typhus

- Elimination of fleas on clothing & bedding using insecticides like 1% Malathion powder
- Apply residual insecticide powder on the floor & bedding to kill hatching fleas.
- Rodent control using chemicals (e.g. warfarin)

For louse borne typhus

- Eradicate all lice on clothing & bedding using insecticides (1% Malathion powder) including all family contacts. DDT is not useful as the lice are often resistant to it

- Wash the patient with soap and water & apply insecticides all over & disinfect clothing with insecticides in a bag or sterilize by autoclaving.
- Protective wearing smeared with insect repellents is recommended for nurses and other attendants

Chemoprophylaxis: Doxycycline 100mg weekly will protect those at risk.

References:

1) Kasper L., Braunwald E. , Harrison's principles of Internal medicine, 16th Edition, Rikettsial diseases, pages 999 - 1007 .

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3. Helminthic Infections

- Intestinal Nematodes
- Tissue Nematodes
- Filariasis and Related Infections
- Schistosomiasis & Other Trematodes
- Cestodes

3.1 Intestinal Nematodes

Learning Objective: At the end of this unit the student will be able to

1. *Define intestinal nematodes*
2. *List the etiologies of intestinal nematodes*
3. *Describe the mode of transmission of intestinal nematodes*
4. *Mention the epidemiology of intestinal nematodes*
5. *Describe the pathophysiology of intestinal nematodes*
6. *Identify the clinical manifestations of intestinal nematodes*
7. *List the complications of intestinal nematodes*
8. *Describe the most commonly used tests to identify intestinal nematodes*
9. *Manage intestinal nematodes at the primary care level with appropriate drugs*
10. *Design appropriate methods of prevention and control of intestinal nematodes*

Nematodes are elongated, symmetric round worms. These can be classified as intestinal or tissue nematodes. Some of the intestinal nematode species are *Strongyloides stercoralis, Enterobius vermicularis, Trichuris trichuira, Ascaris lumbricoides, Necator americanus and Ancylostoma duodenale*. More than a billion people worldwide are infected with one or more species of intestinal nematodes. They are most common in regions with poor sanitation, especially in developing countries.

3.1.1 Ascariasis

Definition: Ascariasis is an infection caused by Ascaris Lumbricoides.

Epidemiology - Ascariasis has a worldwide distribution particularly in regions with poor sanitation. Children frequently acquire ascariasis by the ingestion of embryonated eggs.

Development:- The adult live in the lumen of the small intestine, especially in the jejunum. Eggs reach the external environment with the feces. After ingestion these eggs hatch in the

intestine, liberating minute larvae that rapidly penetrate blood or lymph vessels in the intestinal wall. Some larvae reach the portal circulation & are carried to the liver; others pass through the thoracic duct. They then reach the lung (lung phase), filtered out of blood stream. After increasing in size they migrate to the epiglottis and then down the esophagus to reach the intestine where mating takes place.

***Clinical Features*:**

- During the lung phase patients may develop an irritating nonproductive cough and burning substantial discomfort. Fever is usual during this phase. Chest x-ray may show evidence of pneumonitis (Leoffler's syndrome).
- In established infections, patients are often asymptomatic.
- In heavy infections, particularly in children, large bolus of worms may cause pain and small-bowel obstruction, or they could have chronic abdominal discomfort and growth retardation. A large worm can enter and occlude the billiary tree, causing biliary colic, cholecystits & pancreatitis.

Diagnosis: Most cases of ascariasis can be diagnosed by the microscopic detection of characteristic Ascaris eggs in feces.

Treatment: Mebendazole 100 mg twice daily for 3 days

Piperazine 75mg/kg (max. 3.5g) single dose daily for two days Pyrantel pamoate single dose of 10mg/kg

Albendazole in a single dose of 400mg is also effective.

N.B Mebendazole and albendazole are contraindicated in pregnancy; but pyrantel pamoate and piperazine are safe.

3.1.2 Hookworm

Definition:-It is infection caused by two hookworm species ***Ankylostoma duodenale*** and ***Necator americanus***.

Epidemiology: It is prevalent worldwide. But older children have the greatest incidence and intensity of hookworm infection. It is prevalent in areas with poor sanitary conditions, particularly in relation to human waste disposal. Adults are usually infected when walking or walking bare

footed. Hookworm is one of the most common contributing factors for the development of iron deficiency anemia in developing countries.

***Etiology and development*:** The adults are pink or creamy white. The oval buccal capsule contains two pairs of fused teeth. The male are 8-11mm long; the females, between 10 and 13mm. The adult hookworms live attached to the mucosa of the small intestine. Females liberate eggs into the lumen, which are eliminated with the feces. Under optimum conditions of moisture and temperature they hatch within 24 - 48 hours. They then develop to become infective (or filariform) larvae. When these come into contact with unprotected human skin (usually bare foot), they penetrate the skin layers, enter the blood stream and are transported to the lungs. Then they migrate up the bronchi and trachea and down the esophagus to reach the small intestine where maturity is attained.

Clinical features:

- Most hookworm infections are asymptomatic.
- Infective larvae may provoke pruritic skin lesion at the site of penetration, as well as at subcutaneous migration.
- Infected people may rarely present with mild transient pneumonitis.
- In the early intestinal phase, there may be epigastria pain, inflammatory diarrhea or other GI symptoms.
- The major consequence of chronic hookworm infection is iron deficiency because worms suck blood from the intestine. Anemia usually develops if there is preexisting iron deficiency states like malnutrition and pregnancy.

Diagnosis: Diagnosis is established by the finding of characteristic oval hookworm eggs in the feces. Eggs of the two species are not distinguishable. Anemia of blood loss with Hypochromic microcytic picture is seen in hookworm disease.

Treatment: Several drugs can be used to eradicate hookworm. Commonly used drugs are:

- Mebendazole 100mg twice daily for 3 days
- Albendazole 400mg in a single dose.
- Mild iron-deficiency anemia often can be treated with oral iron alone (ferrous sulphate tabs), until anemia is resolved.

3.1.3 Strongyloidiasis

Definition:- Strongyloidiasis is an infection by the nematode stronyloides stercoralis, the female of which usually is embedded in the mucosa of the small intestine of humans.

Epidemiology: Mainly distributed in tropical areas, particularly in South East Asia, sub-Saharan Africa, and Brazil.

Etiology and development: The parasitic adult female lays eggs that hatch in the intestine. Rhabditiform larvae passed in feces can transform into infectious filariform larvae outside of the host. Humans acquire strongloidiasis when filariform larvae in faecally contaminated soil penetrate the skin or mucous membranes. The larvae then travel to the lungs from the blood stream to reach the epiglottis. They are then swallowed to the small intestine. The minute (2mm-long) parasitic adult female worms reproduce by themselves, parasitic adult males do not exist.

Eggs hatch locally in the intestinal mucosa, releasing rhabditiform larvae that pass with the feces into soil or the rhabditiform larvae in the bowel can develop directly into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to repeat the migration that establishes internal re-infection, called autoinfection. This allows the infection to persist for decades.

Clinical features :

- Mild infections are usually asymptomatic.
- Recurrent urticaria, often involving the buttocks and wrists, is the most common cutaneous manifestation.
- Adult parasites burrow into the duodeno-jejunal mucosa and can cause abdominal (usually midepigastric) pain, which resembles peptic ulcer pain. Nausea, diarrhea, GI bleeding, mild colitis and weight loss can occur.

The autoinfection cycle of strongyloidiasis is normally contained by unknown factors of the host's immune system.

Strongyloidiasis in immune compromised hosts .

- There will be hyper-infection with colitis, enteritis or mal-absorption.

- In disseminated disease larvae invade not only the GIT and lung, but also the CNS, peritoneum, liver and kidneys.
- Bacteremia may develop from enteric bacteria entering through the disrupted intestinal mucosa.

Diagnosis: In uncomplicated stongyloidiasis, the finding of rhabditiform larvae in feces is diagnostic. Serial stool examination may be necessary to detect the larvae. Eggs are almost never seen in stool because they hatch in the intestines.

Treatment: - Even asymptomatic patients should be treated.

- **Thiabendazole**, which is still the drug of choice, is given in a dose of 25mg/kg BID (max. 3g/day) for 3 days. There are however common side effects like nausea, vomiting, diarrhea, dizziness and neuropsychiatric disturbances.
- **Ivermectin** 200μg/kg as a single dose daily for 1 or 2 days is better tolerated. Disseminated cases should be treated for 5-7 days.
- **Albendazole** 400 mg can also be used in simple infections and produces 80% reduction in egg count and 200mg/day oral dose for 3 days gives 100% cure..

3.1.4 Trichuriasis (Whip-worm infection)

Definition: Trichuriasis is an infection of the human intestinal tract caused by the nematode Trichuris trichiura.

Epidemiology:-It is distributed worldwide, but is most abundant in the warm, moist regions of the world, the tropics and subtropics.

Etiology and development:-The parasites have a characteristic whip like shape. The anterior portion is long and thread like; the posterior portion is broader and comprises about 2/5 of the worm. The females are slightly longer than the males, 35-50mm long.

The adult worms reside in the colon and caecum, the anterior portions threaded into the superficial mucosa. Thousands of eggs are laid daily and pass with the feces. They mature in the soil. After ingestion, infective eggs hatch in the duodenum, releasing larvae that mature before migrating to the large bowel. The adult worms may live for several years.

Clinical features: Most infections are asymptomatic. Large worm burden may be associated, especially in children, with diarrhea of long duration, dysentery, mucoid stools, abdominal pain

and tenderness, dehydration, anemia, weight loss and weakness. Rectal prolapse may occur, particularly in children.

Diagnosis: - Diagnosis is reached by demonstration of characteristic lemon-shaped whip worm eggs. Adult worms, which are about 3-5cm long, can be seen on proctoscopy.

Treatment: - Trichuriasis can be effectively treated with mebendazole or albendazol.

Mebendazole 100mg twice daily for 3 days or

Albendazole 4mg/kg as a single dose

3.1.5 Enterobiasis (Pinworm)

Definition:-Enterobiasis is an infection of the human intestinal tract by the pin worm Enterobius vermicularis.

Epidemiology: Enterobiasis is found all over the world. It is more common in temperate countries than tropics.

Tiology and development:-Enterobius vermicularis is a spindle-shaped parasite of humans. The female is 8-13mm long; the male, 2-5mm. Females lay embryonated eggs, which are flattened on one side.

The gravid female worm migrates nocturnally out into the perianal region and releases upto 10,000 immature eggs. The eggs are rapidly infective and are transmitted by hand-to-mouth passage. The larvae hatch and mature entirely within the intestine. Self-infection results from perianal scratching and transport of eggs to the hands or nails and then to mouth. Pinworm infections are very common among family members.

Clinical fearures:

While pinworm infection may be asymptomatic, the most common symptom is the intense nocturnal pruritus ani. This is because of the cutaneous irritation in the perianal region produced by the migrating gravid females and the presence of eggs. Intense pruritus may lead to dermatitis, eczema and severe secondary bacterial infections of the skin. Rarely, pinworms may invade the female genital tract, causing vulvovaginits and pelvic granulomas.

Diagnosis:- Eggs are not found in the stool because they are released in the perineum. Therefore, eggs deposited in the perianal region are detected by the application of clear

cellulose tape to the perianal region in the morning. The tape is then transferred to slide to be seen under a microscope.

Treatment: Keeping personal hygiene is part of the treatment; patients should keep their nails short and wash hands with soap and water after defecation. A single dose of mebendazole 100mg, or pyrantel pamoate10mg/kg, both repeated after 2 weeks is effective. An alternative is piperazine 65mg/kg for 7 days with repeat course after 2 weeks. It is advisable to treat all household contacts.

3.2 Tissue Nematodes

Learning Objective: At the end of this unit the student will be able to

1. *Define tissue nematodes*
2. *List the etiologies of tissue nematodes*
3. *Describe the mode of transmission of tissue nematodes*
4. *Mention the epidemiology of tissue nematodes*
5. *Describe the pathophysiology of tissue nematodes*
6. *Identify the clinical manifestations of tissue nematodes*
7. *List the complications of tissue nematodes*
8. *Describe the most commonly used tests to identify tissue nematodes*
9. *Manage tissue nematodes at the primary care level with appropriate drugs*
10. *Design appropriate methods of prevention and control of tissue nematodes*

Tissue nematodes include *Trichinosis*, *Visceral and Ocular larva migrans*, *Cutaneous larva migrans*, *Cerbral angiostrogliasis* and *Gnathostomiasis*.

3.2.1 Trichinosis

Definition:-Disease caused by the parasite *Trichinella spiralis,* characterized by an acute and rapid course with fever, gastrointestinal symptoms, myalgia and eosinophilia.

Epidemiology:-It is widely spread throughout the temperate regions of the world wherever pork or pork products are eaten. It is enzootic in wildlife in Africa and man is involved sporadically by eating fresh or inadequately cooked pork.

Etiology:-The trichina worm, T.spiralis is a white round worm just visible to the naked eye. Adult male ranges from 1.4 - 1.6mm in length by 40 - 60 μm in diameter; the female is 3-4mm long and about one and one - half times as broad as the male.

Development:-The worm gains entrance to the digestive tract as larvae encysted in muscle tissue. By the time they reach the small intestine they are freed from their cysts, penetrate the duodenum epithelium and mature within a few days. The female are fertilized and produce between 1000 and 1500 larvae during the 3-16 week period they parasitizes man. The larva circulates in the blood. They then invade different tissues mainly the muscles.

Clinical features : -

Twenty-four hours following ingestion of larvae, signs of GI disturbance like nausea, vomiting, diarrhea and abdominal pain may occur. With muscular infiltration there may be periorbital edema, myalgia and persistent fever up to 40.5^{o}c. The last stage is characterized by neurologic symptoms and sometimes myocarditis.

Diagnosis:- Blood eosinophilia develops in > 90% between 2-4 weeks after infection. Serum levels of IgE and muscle enzymes including creatine phosphokinase, lactate dehydrogenase and aspartate aminotransferase are elevated in most symptomatic patients. A presumptive diagnosis can be made based on fever, eosinophilia, periorbital edema and myalgias after a suspected meal. Diagnosis is confirmed by increasing titers of parasite specific antibody or muscle biopsy demonstrating the larvae.

Treatment:- Current antihelminthics are not effective. Most lightly infected patients recover with bed rest, antipyretics and analgesics. Thiabendazole 25-50mg/kg/day for 2-5 days brings down fever and eosinophilia. Mebendazole 300mg daily for 7 days is an alternative. Glucocorticoids (e.g. prednisolone 1mg /kg) are helpful for severe myositis and myocarditis.

3.2.2 Cutaneous Larva Migrans

Cutaneous Larva Migrans ("creeping eruption") is skin eruption caused by burrowing larvae of animal hookworms, usually the dog and cat hookworm (Ancylostoma braziliense). Larvae hatch from eggs passed in dog and cat feces and mature in the soil. Humans become infected after skin contact with soil by penetration. It is prevalent among children and in regions with warm humid climates.

After larvae penetrate the skin, erythematous lesions form along the tortuous tracts of their migration through the dermal-epidermal junction. The larvae advance several centimeters a day. Intensely pruritic lesions occur any where on the body. The adult worm will die without treatment in several weeks.

Diagnosis is readily made clinically.

Treatment is with thiabendazole orally 25mg/kg bid or albendazol 200mg bid for 2 days or topically petroleum jelly for 2-5 days.

3.3 Filariasis

Learning Objective: At the end of this unit the student will be able to

1. *Define filariasis*
2. *List the etiologies of filariasis*
3. *Describe the mode of transmission of filariasis*
4. *Mention the epidemiology of filariasis*
5. *Describe the pathophysiology of filariasis*
6. *Identify the clinical manifestations of filariasis*
7. *List the complications of filariasis*
8. *Describe the most commonly used tests to identify filariasis*
9. *Manage filariasis at the primary care level with appropriate drugs*
10. *Design appropriate methods of prevention and control of filariasis*

3.3.1 Lymphatic filariasis

Lymphatic filariasis is caused by *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori*. While the later two are found in Asia, the former is prevalent in the tropics and subtropics. Therefore, *W.bancrofti* is discussed below.

Definition: Filariasis (bancrofti) is due to the presence of adult *W.bancrofti* in the lymphatic system or connective tissues of man. Many species of Anopheles, Culex, Mansonia and Aedes are vectors.

Epidemiology: It is widespread throughout much of the tropics and subtropics. It is also found in some Far East countries. Complete development of the larval forms has been found to occur in many species of mosquitoes. Generally, W. bancrofti larvae are in lesser number (scarce) in the peripheral blood by day and increase at night.

Clinical features: The most common presentations of the lymphatic filariasis are asymptomatic (or subclinical) microfilaremia, hydrocele, acute adenolymphangitis and chronic lymphatic disease. Most of infected individuals have few symptoms despite large numbers of circulating microfilaria in the peripheral blood. But sub-clinical disease is common with microscopic hematuria and/or proteinuria and in men scrotal lymphangiectasia. Only few patients progress

to the acute and chronic stages of infection. Patients may present acutely with high-grade fever, lymphangitis, and transient local edema. Later patients may have lymphedema (upper and lower extremities) and scrotal swelling.

Diagnosis:-Difficult because microfilaria may not easily be identified. Definitive diagnosis is by demonstration of microfilaria from blood, hydrocele fluid or other body fluids at night.

Treatment: Diethyl carbamazepine (DEC, 6mg/kg daily for 12 days is) the treatment of choice. Albendazol 400mg twice daily for 21 days has been shown to have microfilaricidal activity.

3.3.2 Onchocerciasis

Definition: Onchocerciasis ("river blindness") is caused by the filarial nematode Onchocerca volvulus.

Etiology: The living parasites are white or cream colored and transparent. The males are 19-42 mm long and the females 33 – 50 cm.

Epidemiology:-Infection in humans begins with deposition infective larvae on the skin by the bite of an infected black fly. The larvae develop into adult in subcutaneous tissue and form nodules. About 7 months to 3 years after infection the gravid female releases microfilariae that migrate out of the nodule and through out the tissues. Infection is transmitted to other persons when a female black fly ingests microfilariae from the host's skin and these microfilariae then develop into infective larvae.

Clinical features:

- Following the bite of an infected fly, there is an incubation period of several months before nodules appear. The subcutaneous nodules, onchocercomata, are the most characteristic lesions of onchocerciasis. They usually appear on coccyx, sacrum, thigh and bony prominences.
- But the most frequent manifestations of onchocerciasis are pruritus and rash.

- The skin lesions are characterized by wrinkling of skin and epidermal atrophy that can more often lead to hypopigmentation than hyperpigmentation. Eczematous dermatitis and pigmentary changes are more common in the lower extremities.
- Visual impairment is the most serious complication of onchocerciasis. This is due to intense inflammation that surrounds the dying microfilaria. Early lesions are conjuctivitis with photophobia; sclerosing keratitis occurs in minority of patients, which leads to blindness. Inflammation in the interior eye cause iridocyclitis.
- Patients could have enlarged inguinal lymph nodes (hanging groin).
- Heavily infected patients could have severe wasting.

Diagnosis:-Diagnosis depends on demonstration of the microfilariae in the skin snip or nodules. Microfilariae are rarely found in blood smear, but may be seen in urine.

Treatment:

Chemotherapy is the main treatment.

- ***Ivermectin*** orally in a single dose of 150mg/kg, yearly or semiannually is the treatment of choice. No agent so far eradicates the adult worm. The drug is microfilaricidal and has many advantages: no severe ocular reaction and prevents blindness due to optic nerve disease by 50%, the drug is taken orally only once every 6 – 12 months & inhibits the production of microfilariae by adult female worms for some months.
- Ivermectin is contraindicated if there is co-infection with loa loa, inn pregnant or lactating women and children under the age of 5 years.
- Antihistamines should be given for the pruritus.

Prevention

- Personal exposure in endemic areas can be reduced by avoiding black fly localities and by protective clothing. Repellents are of value only for short periods as they are washed off by sweat.
- Control programmes (2 in Africa and one in America) have covered over 99% of all population living in endemic areas.

The control of onchocerciasis today is based on 2 strategies:

- Vector control by spraying insecticides. Onchocerciasis control Programme in West-Africa used this strategy

- Large scale Ivermectin chemotherapy is the main strategy being used by Onchocerciasis Elimination Programme in the Americas (OEPA) and African Programme for Onchocerciasis control (APOC)

3.4 Trematodes

Trematodes or flatworms are a group of morphologically and biologically heterogeneous parasitic helminthes that belong to the phylum platyhelminthes. Human trematode infections are classified according to the site they involve; the adult flukes may involve blood, biliary tree, intestines and lungs. Blood flukes are schistosoma mansoni, S.haematobium, S.japonicum, S. intercalatum, and S. mekongi. Biliary (hepatic) flukes are opisthorchis viverini, clonorchs sinensis and fasciola hepatica. Intestinal flukes are Fasciolopsis buski, and Heterophyes. Finally, lung flukes are paragonimus westermani. Because of its public health importance, only schistosomiasis is discussed here.

3.4. 1 Schistosomiasis

Learning Objective: At the end of this unit the student will be able to

1. *Define schistosomiasis*
2. *List the etiologies of the different types of schistosomiasis*
3. *Describe the mode of transmission & the life cycle of schistosomiasis*
4. *Explain the risk behavior of transmission of schistosomiasis*
5. *Mention the epidemiology of schistosomiasis*
6. *Explain the pathogenesis of schistosomiasis*
7. *Identify the clinical features of the different schistosomiasis*
8. *List the common complications of schistosomiasis.*
9. *Describe the most commonly used tests for the diagnosis of schistosomiasis*
10. *Make an accurate diagnosis of schistosomiasis*
11. *Manage schistosomiasis at the primary care level with appropriate drugs*
12. *Design appropriate methods of prevention & control of schistosomiasis*

Definition

Schistosomiasis (also known as Biliharziasis) is a group of diseases caused by the genus Schistosoma affecting mainly the gastrointestinal and genitourinary organs.

Etiology and life cycle: Schistosomiasis in man is caused by five species of Schistosoma

S. mansoni

S. haematobium

S. japonicum- in southeast Asia

S. makongi- in southeast Asia (makongi valley Laos, Cambodia)

S. intercalatum - endemic in Congo basin

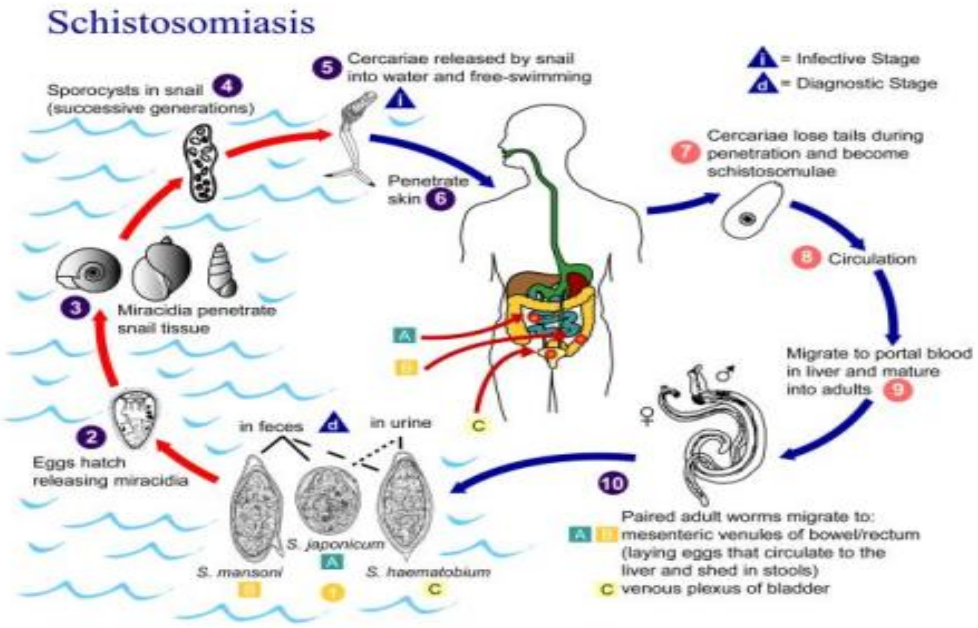
The first three are common causes of schistosomiasis. S. haematobium is the cause of urinary schistosomiasis and all the rest cause intestinal schistosomiasis.

Life cycle

Man is the definitive host where sexual reproduction takes place after cercarial entry by skin penetration and snails are intermediate hosts in which asexual regeneration continues. Each species of Schistosoma has a specific snail host i.e.

S. mansoni	-Biomphalaria species
S. haematobium	- Bulinus species
S. japonicum	- Onchomelania species

Life cycle of Schistosomiasis



Epidemiology

- Distribution is world wide where appropriate snails are present. *S. mansoni* is reported from Africa, Asia, Central and S. America and Europe, and *S. haematobium* is endemic in most Africa and West Asia. The other three species have localized distribution. In Ethiopia, only *S. mansoni* and S. *haematobium* are endemic. S. mansoni has a wider distribution in the lower highland areas of Ethiopia between 1000- 2000 meter altitude. *S. haematobium* is endemic in low lands of Ethiopia.
- It is transmitted by cercarial skin penetration which requires contact with water bodies containing cercaria escaping from appropriate snail host. This is encouraged by limited sanitary facilities (lack of safe and adequate H_2O supply and latrines) substandard hygienic practices, use of water for irrigation, ignorance, poverty and population movements.

Clinical manifestations

Intestinal schistosomiasis is caused by all human Schistosoma except *S. haematobium*, which is the only cause for urinary schistosomiasis. It affects the large bowel, the liver(in the intestinal form), distal colon and rectum, and manifestations are dependent on the stages of infection. The 1st two stages are the same for all species of Schistosoma:-

a) Stege1. **Swimmer's itch (stage of Invasion)**: This is the first clinical sign of acute infection appearing soon after exposure, usually with in 24 – 48 hrs, and characterized by itching at sites of cercarial entry commonly known as **swimmer's itch**. It is seen in new comers and not common in indigenous people.

b) Stege2. Acute stage (also called toxemia stage/ **Katayama syndrome** in Asia)

It is an early allergic manifestation to egg deposition (3 – l0 wks) in response to massive antigenic stimulus of eggs and include fever, headache, chills, myalgias malaise, profuse diarrhea, nausea and vomiting. Patient may have generalized lymphadenopathy, hepatosplenomegally, urticaria and leucocytosis with marked eosinophilia. Severity depends on intensity of infection, and tends to be mild in indigenous population.

c) Stage 3 &4 (**Chronic stage**) occurs 3 months to several years later, coincides with deposition of eggs in the tissues. The clinical picture represents the effect of the pathologic lesions caused by the eggs on the urinary and gastrointestinal systems. Thus urinary and intestinal Schistosomiasis are different in their manifestations, as described below.

d) Stages 3&4 intestinal Schistosomiasis

The disease is very light and symptom-less for months, and then presenting with recurrent diarrhea with blood and lethargy. They may have intestinal polyps, and progressive fibrosis of the intestinal wall leading to formation of strictures but intestinal obstruction is very rare. Moreover, granulomatous hepatitis followed by progressive peri-portal fibrosis (also called pipe stem fibrosis) may develop resulting in portal hypertension with associated splenomegally, ascites and esophageal varices that occasionally may bleed.

e) Stages 3 and 4 urinary Schistosomiasis

Deposition of eggs in the wall of the urinary bladder induces the formation of pseudo tubercles and epithelial hyperplasia, with subsequent fibrosis and calcification causing dribbling, incontinence, frequency, dysuria and hematuria. Chronic infection leads to obstructive uropathy, hydronephrosis, chronic pyelonephritis, renal failure and contraction of the bladder.

In rare instances gonads, CNS (brain, spinal cord), lungs and endocrine organs can be involved.

Laboratory Diagnosis

- Identification of the characteristic ova

In stool or urine by

  - Direct smear method; easy but light infection can be missed
  - Sedimentation / Concentration method
  - In rectal snip/bladder biopsy sample if it cannot be detected in the stool or urine.

- Seroimmunological diagnosis lacks specificity,

Clinical diagnosis

- **For intestinal Schistosomiasis**
  - Sigmoidoscopy and rectal snip identifies lesions and ova of the parasite
  - Ultrasound of liver and spleen to demonstrate peri-portal fibrosis and spleen enlargement
  - Liver biopsy
- **For urinary schistosomiasis**
  - Cystoscopy - demonstrates fibrosis and calcification of the bladder
  - Bladder biopsy and histology demonstrates ova in biopsy sample
  - Radiological

- Plain abdominal X- ray may detect calcification of bladder
- Intravenous Pyelogram-to see for the presence of obstructive uropathy
- Ultrasound of the kidneys and ureter

Treatment

Drug treatment is both safe and effective,

- **Praziquantel :** has wide spectrum, effective against all species of Schistosoma, single oral dose, has high cure rate

  Dose: *S. mansoni and S. haematobium* = 40mg/kg orally once

  S. japonicum = 60mg/kg orally once
- **Metrifonate** is effective against *S. haematobium.*

  Dose: 7.5 – 10mg/kg in 3 doses at 2 wks interval
- **Oxaminoquine** is effective against *S. mansoni*

  Dose: 15mg/kg orally once for sensitive strains

  In Ethiopia 40mg/kg orally once

Prevention and control requires multidisciplinary approach

- Environmental sanitation avoidance of pollution of surface water
  - Provision of latrine and sanitary waste disposal
  - Prevention of human contact with infected water
  - Provision of safe and adequate water
  - Protective clothing when contact is unavoidable
  - Health education to reduce contact with infected water bodies
- Elimination of the disease in the reservoir by chemotherapy
  - Case finding and treatment and mass (community) treatment in selected population
- Snail control
  - Physical control-alteration of habitat,eg removal of vegetation, drainage of swamps etc
  - Chemical control (moluscicides) Yurimin, Frescon, “Endod“ (phytholacca dedocandra)
  - Biological control- Fish or other snails that feed on vector snails

References:

1. Schistosomiasis in Ethiopia , Patho Biology Department AAU
2. Kasper L., Braunwald E. , Harrison's principles of Internal medicine, 16th Edition, Schistosomiasis , pages 1266-1271.

3.5 Cestodes

Learning Objective: At the end of this unit the student will be able to

1. *Define cestodes*
2. *List the types of cestodes and their etiologies*
3. *Describe the mode of transmission of cestodes*
4. *Explain the risk behavior for the transmission of cestodes*
5. *Mention the epidemiology of cestodes*
6. *Identify the clinical features of cestodes*
7. *List the common complications of infection by cestodes*
8. *Describe the most commonly used tests for the diagnosis of cestodes*
9. *Make an accurate diagnosis of cestodes*
10. *Manage cestodes at the primary care level with appropriate drugs*
11. *Design appropriate methods of prevention and control of cestodes*

Cestodes or tapeworms are segmented worms. The tapeworms can be divided into two.

- In one group the definitive hosts are humans, these include Taenia saginata, Diphyllobothrium, Hymenolepsis and Dipylidium Canium.
- In the other group, humans are intermediate hosts. These are Echinococcosis, Sparganosis and Coenurosis.
- Humans can be a definitive or intermediate host to T.solium.

3.5.1 Taeniasis saginata

Definition:-Taeniasis saginata or beef tapeworm infection is caused by the presence of the adult beef tapeworm, T.Saginata, in the intestine of humans.

Distribution:- It is found all over the world. It occurs in all countries where raw meat is ingested. It is prevalent in sub-Saharan Africa and the Middle East. Ethiopia is one of the heavily affected countries.

Etiology and Epidemiology: T.Saginata is a large tapeworm usually 5-10 meters in length. The scolex carries four round suckers. Behind the scolex there is a short neck from which proglottids (segments) form. As each proglottid matures, it is displaced further back from the neck by the formation of new, less mature segments. Humans are the only definitive host. Eggs deposited on vegetation can persist for months or years, until ingested by cattle. Embryo

from cattle intestine migrates to the muscle and transform into cysticercus. When eaten raw or undercooked, this infects humans.

Clinical features : Usually patients are asymptomatic. Often infection is detected when patients pass proglottids with stool or alone. Proglottids are motile and this causes perianal discomfort during discharge. Mild abdominal pain, nausea, anorexia and weight loss can occur.

Diagnosis: The diagnosis is reached by demonstrating the eggs or proglottids in the stool.

Treatment: Treatment of choice is prazequantel 5 -10 mg/kg in a single dose.

Niclosamide as a 2 g single morning dose before breakfast is an alternative.

3.5.2 Taeniasis Solium:

It is caused by T.solium from eating raw or undercooked pork.

Etiology: The adult tapeworm resides in the upper jejunum, similar to taenia saginata. Its scolex attaches to intestinal wall by both sucking disk and two rows of hooklets. Life cycle is similar to beef tapeworm. However, both the adult tapeworm and the larvae (Cysticerca) infect people.

Clinical features : Mostly patients are asymptomatic; but they could have epigastric discomfort, nausea and weight loss. Patients may note passage of proglottids. When infected with cysticerica (cysticercosis), they are distributed all over the body. The major manifestations come from the CNS with seizures, headache, raised intracranial pressure, mental changes etc.

Diagnosis: The diagnosis of intestinal T.solium infection is made by the detection of eggs or proglottides. Diagnosis is difficult in cysticercosis, which is done by different clinical and laboratory criteria.

Treatment: Intestinal *T.solium* infection is treated with a single dose of prazequantel 5-10 mg/kg, this treatment may be complicated by development of CNS inflammation if cysticercosis co-exist. If patients develop CNS symptoms, refer them to a hospital.

3.5.3 Hymenolepis nana (Dwarf tapeworm)

Etiology: Dwarf tapeworm is 25-40mm in length by 1mm in breadth. The scolex bears four small suckers.

Epidemiology: It is distributed all over the world.

This tapeworm doesn't require intermediate host. Hatching of eggs occurs in the small intestine where they penetrate the villus and become cysticercoid.

Eventually the parasites breakout in to the lumen of the gut and reach maturity. Infection is prevalent in children.

Clinical features: Most infections are asymptomatic. Severe infections may manifest with abdominal pain, anorexia and diarrhea.

Diagnosis: Diagnosis is based upon demonstration of the eggs in the stool.

Treatment: - The treatment of choice is praziquantel 25 mg/kg as single dose.
A course of niclosamide for 7 days is also effective.

3.5.4 Diphyllobothriasis (fish tape worm):-

Diphyllobothriasis is infection caused by adult Diphyllobothrium latum. It is acquired from eating raw fish.

Etiology: It is mostly found in Europe and Northern hemisphere. It is the longest tapeworm reaching up to 25 meters.

Clinical: Many people are asymptomatic. But patients could have abdominal pain, loss of appetite, anorexia, nausea, diarrhea or loss of weight. Since this tapeworm consumes a lot of vitamin B12 and interferes with its absorption, it can cause vitamin B12 deficiency; and some patients develop megaloblastic anemia.

Diagnosis: Diagnosis is reached by demonstration of characteristic eggs in the stool.

Treatment:

- Praziquantel 5-10 mg/kg once is very effective.
- Vitamin B12 deficiency should be treated if present.

N.B further reading Module on intestinal parasitosis, by Health Science College, Hawassa University

3.6 Leishmaniasis

Learning Objective: At the end of this unit the student will be able to

1. *Define leishmaniasis*
2. *Classify leishmaniasis*
3. *List the etiologies & animal reservoirs of the different types of leishmaniasis*
4. *Describe the mode of transmission leishmaniasis*
5. *Explain the epidemiology of leishmaniasis*
6. *Describe the pathophysiology of visceral leishmaniasis*
7. *Identify the clinical manifestations of the different types of leishmaniasis*
8. *List the complications of visceral leishmaniasis*
9. *Describe the most commonly used tests for the diagnosis of leishmaniasis*
10. *Make a presumptive diagnosis of leishmaniasis*
11. *Refer suspected cases of leishmaniasis to hospitals for investigation & treatment*
12. *Design appropriate methods of prevention andcontrol of leishmaniasis*

Definition: is an infectious disease caused by the protozoa called *Leishmania*

Classification of leishmaniasis

There are three major clinical forms of leishmaniasis**:**

- **Visceral leishmaniasis**
- **Cutaneous leishmaniasis**
- **Mucocutaneous leishmaniasis**

Etiologic Agents

The different clinical forms of leishmaniasis (listed above) are caused by different species of leishmanial parasites which are listed under each of these diseases. The parasites are seen in two forms

- Leishmanial form:- (amastogote) this is non flagellate form seen in man and extra human vertebrate reservoir
- Leptomonad forms (also called promastigotes) are flagellated forms

The parasite is transmitted by the bite of vectors of the species phlebotomus, Sand flies

Life Cycle of Leshimaniasis

- Transmitted by the bite of an infected female phlebotomine Sand fly, the leishmaniases are globally widespread diseases. Sand flies are primarily infected by animal reservoir hosts, but humans are also a reservoir for some forms. Animal Reservoirs: include Rodents - Commonly in East Africa, Ethiopia, the Sudan and Kenya and Canines - Mediterranean and Asia.
- The life-cycle starts when a parasitized female sandfly takes a blood meal from a human host. As the sandfly feeds, promastigote forms of the leishmanial parasite enter the human host via the proboscis. Within the human host, the promastigote forms of the parasite are ingested by macrophage where they metamorphose into amastigote forms and reproduce by binary fission. They increase in number until the cell eventually bursts, then infect other phagocyctic cells and continue the cycle.
- The infected host is bitten by another female sandfly. Parasites are picked up by the fly during the blood meal. The parasites are transformed inside the fly and delivered to a new host, and the life-cycle continues

Fig 3.6.1 Life cycle of Leshimania

Visceral Leishmaniasis (Kala Azar)

Visceral leishmaniasis is a chronic systemic disease caused by ***L. donovani.*** It is characterized by chronic irregular fever, profound wasting, debility and hepatosplenomegally.

Epidemiology

Visceral leishmaniasis affects many countries in Africa, mainly Ethiopia and the Sudan the Middle East, Southern soviet union, India and S. America. It is endemic in low land Ethiopia mainly North Western Ethiopia (Metema, Humera), Gikawo (Gambella), lower Omo river basin and in the south Woito and Segan river basin, Moyale and lower Genale river. The disease is becoming a common opportunistic infection in HIV/AIDS.

Transmission

The commonest way of transmission is by inoculation of promastigotes into humans by the bite of sand flies which breed in termite hills and forests. The source of the aflagellate forms may be either humans or extra human vertebrate reservoirs, and the disease may have life cycles that involve humans and sand flies only, or humans, sand flies and extra human vertebrate reservoirs together. Rarely transmission may occur via blood transfusion and injections.

Pathogenesis

The common site of entrance is the skin where primary cutaneous lesion appears at the sites of sand fly bite. The lesion is tiny and may pass unnoticed. This is also called primary leishmanioma. Here a cellular reaction by lymphocytes and plasma cells develop around the amasitigote-filled histiocytes in the dermis. As immune response develops epitheloid and giant cells appear, to be followed in some by healing.

In others usually 4-6 months later amastigotes escape to the blood in macrophages, hematogeneous spread occurs and colonize the cells of reticuloendothelial system, where they multiply further and released after rupture of the cells and transported to new cells. The cells affected include that of spleen, liver, bone marrow and lymphatic glands, where the parasite multiplies and cause overcrowding of cells and as a result these organs are enlarged.

The spleen is grossly enlarged with smooth capsule initially, which become thickened & nodular as disease progresses. The involvement of the bone marrow leads to the development of pancytopenia. The liver with its Kuppfer cells packed with amastigotes is enlarged & progress to cirrhosis. The lymphatic glands are enlarged & congested especially the mesenteric group.

Clinical Features

- Incubation period usually varies from weeks to months but can be as long as years.
- Visceral infections remain sub clinical or become symptomatic with acute, sub acute or chronic course.
- The onset is often gradual but can also be sudden with high grade fever (intermittent or remittent) lasting for 2-6 weeks and occasionally longer. Waves of fever are separated by afebrile periods.
- In those with gradual onset in endemic areas discomfort below the left costal margin is common due to enlarged spleen and have cough, epistaxis and diarrhea.
- The patient will be markedly emaciated, with hepatosplenomegally, generalized peripheral lymphadenopathy and marked pallor in the late stage of the disease.
- Edema of the legs, brittle dry hair, hemorrhages from any site (gum, skin etc) with purpura and petechiae of the skin may occur.
- Some patients develop post - Kala- Azar derma leishmaniasis after months or years of treatment for VL.

Diagnosis

- **Definitive diagnosis is based on demonstration of the Parasite**
    - Giemsa stained smear of peripheral blood (in Indian form) and tissue touch preparation of organ aspirates and examined by light microscopy.
    - Culture of tissue aspirates taken from the spleen, BM, liver or lymph node with the corresponding yield of 95%, 85%, 75%, 60% respectively, using different media (NNN or Schneider insect media)
- ***Serologic diagnosis*** - ELISA or DAT, both 100% sensitive & specific
- **Montenegro skin test** - negative in visceral leishmaniasis, becomes positive 6-8 wks after recovery.
- **CBC** - Pancytopenia (anemia, leucopoenia, thrombocytopenia)

Management

Patients need hospitalization for proper treatment and follow up.

- **Supportive treatment**
  - Blood transfusion to correct anemia
  - Treat any additional infection
  - Correct malnutrition
- **Definitive treatment**

  Pentostam / Sodium Stibogluconate: IV, IM 20mg sb/kg per day for 28 days

  For relapse or incomplete cure the same drug can be used for 40-60 day

  If resistant to the above drug use alternative drugs

  Amphotercine B lipid formulation: IV 2- 5mg/kg per day 5-25 weeks

  Petntamidine: IV, IM 4 mg/kg per day for 3-4 weeks

Prevention measures should include

- Reduction of human contact with sand flies by using
  - Insecticide impregnated bed nets
  - Wearing protective clothing and covering as much skin as possible
  - Chemical repellents applied on exposed skin before hours of sandfly activity (dusk and night) are effective.
  - Combustion of permethrin containing mosquito coils is also effective
  - Screening windows and doors
- Reduction of sand fly population by using insecticides DDT, Malathion
- Control of reservoir - dogs rodent
- Construct huts and camps away from breeding sites (termite hills and forests).
- Destroy sand fly breeding sites

Cutaneous Leishmaniasis (oriental sore)

The skin is one of the organs commonly affected by leishmania. Following the bite of sand flies, leishmania multiply in the macrophages of the skin. Single or multiple painless nodules occur on exposed areas (mainly the face) within one week to 3 months of the bite. The nodules may enlarge and ulcerate with erythematous raised border and overlying crust which may spontaneously heal over months to years. Different clinical patterns are described depending on the etiologic agents as follows:-

Table I- 3.6-1: Important causes of cutaneous leishmaniasis

In the Old World			
Leishmania Species	**Distribution**	**Reservoir**	**Clinical Pattern**
L.major & L.tropica	Russia & Eastern Europe middle east, the Mediterranean sub-Saharan& west Africa.	Desert rodent for L.major dog& humans for L.tropica	Spontaneous healing with scaring
L. ethiopica	Highlands of Ethiopia & Kenya	Hyrax	Spontaneous healing with in 6 mo
In the New World			
L. amazonensis			Diffuse cutaneous leishmaniasis resembling lepromatous leprosy (but spares the nasal septum)
L. peruviana	Cooler climates(Andes)		Single or multiple ulcers(Uta),heal spontaneously
L. mexicana	Mexico, Guatemala Brazil, Venezuela & Panama		Infection of Pinna (chiclero's ear) Causes destruction of Pinna lesion persisting for more than 20 yrs.

Investigation for Diagnosis

- Giemsa staining of smear from a split skin: This demonstrates leishmania in 80% of cases
- Culture followed by smear

- Leishmanin skin test is positive in over 90% of cases although it is negative in diffuse cutaneous leishmaniasis.

Treatment

Small lesions don't require treatment. However large lesions or those on cosmetically important sites require treatment either

- **Locally** - by surgery, curettage, cryotherapy or hyperthermia (40-42^{0}c) or
- **Systemic therapy:** with drugs like Pentostam.
  - N.B. Treatment is less successful than visceral leishmaniasis as antimonials are poorly concentrated in the skin L. ethiopica is resistant to antimonials.

Mucocutaneous Leishmaniasis

- It is caused by ***L. braziliensis***, and commly seen Latin America (Brazil, Ecuador. Bolivia, Uruguay and Northern Argentina)
- In the early stage it affects the skin, but in secondary stage of the disease it involves the upper respiratory mucosa.
- Initially painful, itchy nodules appear on the lower limbs and then ulcerate with lymphangitis. Tue lesion may heal spontaneously in 6 months.
- In about 40% of patients, secondary lesions appear several years later at the mucocutaneous junctions of nesopharynx. This leads to nasal obstruction, ulceration, septal perforations and destruction of the nasal cartilage called Espundia.

Diagnosis is difficult as there are a few leishmania in the lesions

- Leishmanin skin test is often positive
- Antibody tests (DAT, ELISA) are often positive

Treatment: Requires systemic antimonials (Pentostam) but relapses are common. Amphotericin is sometimes used. Death usually occurs from secondary bacterial infection

References:

1. Kasper L., Braunwald E. , Harrison's principles of Internal medicine, 16th Edition, Leshimaniasis , pages 1233-1237.

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EPHTI

4. Tuberculosis

Learning Objective: At the end of this unit the student will be able to

1. *Define Tuberculosis*
2. *List the etiologic agents for Tuberculosis*
3. *Describe the mode of transmission of Tuberculosis*
4. *Understand the epidemiology of Tuberculosis*
5. *Describe the pathophysiology of Tuberculosis*
6. *Identify the clinical manifestations of Tuberculosis*
7. *List the complications of Tuberculosis*
8. *Describe the most commonly investigations for the diagnosis of Tuberculosis*
9. *Make an accurate diagnosis of Tuberculosis*
10. *Understand the different treatment categories of Tuberculosis be able to categorize any type of Tuberculosis*
11. *Understand the different case definitions of tuberculosis*
12. *Manage most cases of tuberculosis appropriately*
13. *Refer complicated cases of Tuberculosis diseases to hospitals for better management*
14. *Design appropriate methods of prevention and control of Tuberculosis*

Definition: Tuberculosis is a Chronic necrotizing disease caused by Mycobacterium tuberculosis complex. It usually affects the lungs but almost all organs can be affected. Thus it is conveniently classified into:

- ***Pulmonary TB (PTB)***: accounts for 80% of all TB cases.
  Smear-positive PTB: 75-80% of all PTB cases
  Smear-negative PTB: 20-25% of all PTB cases
- ***Extra-pulmonary TB (EPTB)***: accounts for 20% of all TB cases.

Etiologic Agent: Mycobacterium belongs to the mycobacteriaceae family. The species commonly involved are M. tuberculosis, M.bovis, M. africanum and M.microti. But of all, M.tuberculosis is by far the commonest. M. tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring about 0.5μm by 3μm. The bacterium is demonstrated by acid fast staining technique.

Epidemiology:-

- Tuberculosis is one of the most prevalent diseases in the world. About one-third of the world's population is infected with tuberculosis and thus at risk of developing active disease (TB). It is estimated that 8.4 million people develop active TB every year and 2.3 million die. More than 90 % of TB cases and deaths occur in developing countries and 75 % of cases are in the most economically productive age group.
- TB has been recognized as major cause of morbidity and mortality in Ethiopia. According to a report from Ministry of health TB is 3rd leading cause of hospitalization and 1st leading cause of Hospital death. WHO Estimates Incidence of TB in Ethiopia is 356 per 100,000 /yr and the incidence Smear positive TB is 155 per 100,000/year.
- In the year 2001 the TB leprosy control program (TLCP) registered 94,957 cases of TB from DOTS implementing areas.
- Coinfection with HIV significantly increases the risk of developing Active TB and HIV has become the most important risk factor to develop active TB. In HIV- infected persons the risk of developing TB is increased by more than 10 times compared to those who are HIV negative. It is estimated that about 40% of adult TB cases in urban areas are HIV-positive. The incidence and prevalence of tuberculosis, in recent years has doubled or tripled because of the HIV pandemic, especially in developing countries. It is also shown that active tuberculosis can result in rapid progression of HIV infection in a patient.
- Multi-drug resistant TB which often results from poor management is becoming a serious concern in many countries.

Transmission

Adults with smear positive TB such as cavitory TB and Laryngeal TB are the sources of infection. Patients who are culture-negative pulmonary TB and extra pulmonary disease are not infectious.

M. tuberculosis is commonly transmitted from a patient with infectious tuberculosis to a healthy individual through

- Inhalation of droplets excreted via coughing, sneezing or speaking.
- Un-boiled milk could also transmit M. bovis, but the incidence seems to be decreasing because of health education on boiling or pasteurizing milk.

Factors that facilitate transmission of pulmonary tuberculosis are

- Infectivity of the contact (patients with heavy bacterial load)
- Environment: overcrowding
- Duration of contact (prolonged exposure)
- Intimacy (how close the source and the subject are)

Patients who acquire the infection may not develop the disease. The rate of clinical disease is highest during late adolescence and early adulthood, but the reasons are not clear. Especially young women are affected more than men.

The presence some disease conditions increase the likely hood of developing active TB (Clinically over disease).

- The commonest is co-infection with HIV, which suppresses cellular immunity.
- Hematologic and other malignancies : lymphoma, leukemia, malignancies,
- Chronic renal failure
- Diabetes mellitus
- Immune suppressive drugs like long-term corticosteroids (e.g. prednisolone)
- Old age because of decreased immunity.
- Malnutrition is a very important factor for the development of disease.

Pathogenesis

M. tuberculosis enters the body mostly via respiratory tract through coughed out droplets from an infectious patient.

M. tuberculosis interacts with host immune system immediately after entry. Activated alveolar macrophages ingest the bacilli; after which they release chemicals to activate other immune system components and try to control the infection or multiplication of bacilli. This process will bring about cell - mediated immune response. These activated cells aggregate around the lesion and the center becomes necrotic, soft cheese like material called ***caseous necrosis***. The center, however, may still contain live bacteria that become dormant. These bacteria will flare up and multiply when the person's immunity is depressed. But if the bacteria inside the macrophage multiply rapidly, they will kill the macrophage and are released but to be taken up

by other macrophages again. If this process is not arrested, patients may develop disseminated infection.

Clinical Manifestations

***Pulmonary Tuberculosis*: -** This can be classified as primary or post primary (Secondary).

Primary disease: Clinical illness directly after infection is called primary tuberculosis; this is common in children <4 years of age. Thus, it results from an initial infection.

- Frequently it involves the middle and lower lung zones.
- In the majority it heals spontaneously leaving a healed scar on the lung called *Ghon lesion*.
- It may be contained by immunity into dormant stage only to flare up in immuno-compromised state.
- In children or in immune compromised individuals the disease is usually rapid involving the lungs, pleura and mediastinal lymph nodes. It may disseminate into the blood stream and cause milliary tuberculosis or TB meningitis that may be rapidly fatal.

Post primary disease: -If no clinical disease is developed after the primary infection, dormant bacilli may persist for years or decades before being reactivated, when this happens, it is called secondary (or post primary) tuberculosis. Therefore this is from endogenous reactivation of latent infection.

- It is more common in adults, and typically involves the apical lobes. But any portion of the lungs may be involved. The disease could extend from small infiltrates to large cavitory lesions. Patients with cavitory lesion expectorate tuberculosis bacilli with sputum.
- Early in the course patients may have intermittent fever, night sweats, weight loss, anorexia and weakness. Most patients have cough, which may be dry at first, but later becomes productive of whitish sputum; it is frequently blood streaked. Patients may have exertional dyspnea.
- **Physical examination** may reveal a chronically sick patient with pallor and clubbing. Inspiratory crepitations are seen in some cases.

- **Laboratory findings** may include raised ESR, anemia or leukocytosis. Sputum examination may be positive for AFB. Chest x-ray findings are non-specific; infiltrations, consolidation or cavitory lesions may be present.

Extra-pulmonary Tuberculosis:-Commonly affected organs are lymph nodes, pleura, meninges, genitourinary tract, bones and joints, and peritoneum.

Lymph-node tuberculosis (TB lymphadenitis):-

- It is seen more in HIV patients.
- The commonest sites are cervical and supraclavicular.
- Lymphnodes are typically matted and firm, sometimes pus may be discharging.
- The diagnosis is made by fine needle aspiration and/or lymph node biopsy.

Pleural tuberculosis:-

- Pleural involvement may be asymptomatic or patients could have fever, pleuritic chest pain and dyspnea.
- On physical examination, typically there will be decreased tactile fremitus, dullness and decreased breath sounds on the affected side.
- Fluid should be aspirated from pleural space (thoracentesis) and analyzed.
- Chest x-ray is also helpful in diagnosis; it may show homogenous opacity with meniscus sign.
- Empyema (pus in the pleural space) may complicate tuberculosis occasionally.

Genitourinary tuberculosis:

- It can involve any part of the system.
- Dysuria, intermittent hematuria and flank pain are common presentations. But it may be asymptomatic for a long period of time.
- Urinalysis shows pyuria and hematuria without bacteria in majority of cases (commonly called sterile pyuria). Diagnosis may be reached by culturing urine repeatedly for M.tuberculosis.
- It affects more females and may present as infertility or pelvic pain.

Skeletal Tuberculosis:-

- It is usually reactivation of hematogenous site or extension from a nearby lymph node. The most common sites are spine, hips and knees.
- ***Spinal tuberculosis is called Pott's disease*** or tuberculous spondylitis. In adults, lower thoracic and lumbar vertebrae are commonly affected. Patients may present with swelling and pain on the back with or without paraparesis or paraplegia due to cord compression.
- Tuberculosis in other bones or joints usually present with pain and swelling.
- Joint tuberculosis: - Any joint can be affected but weight bearing joints; particularly the hip and knee joints are commonly involved. Patients present with progressive joint swelling, usually with pain and limitation of movement. If left untreated, the joint may be destroyed.

Tuberculosis Meningitis:-

- It is commonly seen in children and immuno-compromised people particularly patients with HIV.
- More than half have evidence of disease in the lungs.
- Patients with TB meningitis present with headache, behavioral changes and nuchal rigidity for about two weeks or more. Patients may have cranial nerve paralysis and seizure.
- **Cerebra spinal fluid analysis** is the most important modality to diagnose TB meningitis. CSF examination shows increased WBC count, predominantly lymphocytes, and high protein and low glucose content. But any of theses could be normal in the presence of the disease. AFB can be seen in sediment CSF in only 20% of cases; this percentage increases if examined CSF volume is increased. Culture may be positive in about 80%, but it takes 4 to 6 weeks to grow.
- Patients should be referred to a hospital if TB meningitis is suspected.

Gastro Intestinal Tuberculosis:-

- Tuberculosis can affect anywhere from the mouth to the anus.
- Bacteria could reach GI by swallowing sputum, hematogenously or by ingesting raw milk. The commonest sites are terminal ileum and cecum.

- Abdominal pain, diarrhea, symptoms of intestinal obstruction and hematochezia (frank blood on stool) may be the presenting symptoms. There could be associated fever, night sweats, weight loss and anorexia. There could be a palpable mass in the abdomen. Patient could have involvement of the peritoneum, liver and spleen.
- ***Tuberculos peritonitis*** arises from ruptured abdominal lymph node or hematogenous dissemination. Patients usually present with abdominal swelling and pain, weight loss, fever and night sweating. Aspiration of peritoneal fluid (paracenthesis) reveals exudative fluid with many WBC, predominantly lymphocytes. AFB is rarely positive and culture positivity is very low.
- Involvement of the liver and spleen is part of disseminated tuberculosis. Patients will present with hepatomegaly and/or splenomegaly. There could be evidence of involvement of other organs.

Pericardial Tuberculosis (TB pericarditis):

- It is frequently seen in patients with HIV.
- Patients usually present with fever, retro-sternal pain, cough, dyspnea and generalized edema because of pericardial effusion. Cardiac tamponade may appear later
- Constrictive pericarditis may develop as a complication of TB pericarditis even after treatment and patients can present with symptoms and signs of right sided heart failure.
- Diagnosis is usually reached by analyzing the pericardial effusion, which is always done in hospitals. It may show lymphocytosis, but yield for AFB is low.
- Chest x-ray may show enlarged heart shadow, which suggests effusion. Ultrasound should be done when available and it demonstrates effusion.

Milliary tuberculosis:-

- This is secondary to hematogenous dissemination of the bacilli.
- It is more common in children and immuno-compromised patients.
- Manifestations are nonspecific with fever, night sweats, anorexia, weakness, and weight loss. Patients may or may not have respiratory symptoms.
- Physical examination findings include seriously sick patient with hepatomegaly, splenomegaly and lymphadenopathy.
- Since symptoms and signs are not specific, high index of suspicious is required for the diagnosis.
- Chest x-ray usually shows milliary pattern of infiltration bilaterally (milliate like lesions, “dagussa” in Amharic).

Diagnosis

Clinical suspicion is very important for the diagnosis of tuberculosis. Patients who have suggestive symptoms and signs for tuberculosis should undergo further tests.

- **AFB Microscopy :**

AFB is found on microscopy from specimens like sputum, pleural, peritoneal and cerebrospinal fluid and body discharges, but the yield is different. However, definitive diagnosis depends on detection of *M. tuberculosis* from a culture of specimen.

Sputum examination is extremely important in patients who have sputum production.

- AFB stain should be done 3 times in 2 consecutive days (spot - early morning - spot).
- Sputum smear is said to be positive when at least 3 AFB are seen.
- Smear positive TB is diagnosed when at least 2 smears are positive or one smear positive plus suggestive chest x-ray finding.
- If all 3 sputum smears are negative and the patient has suggestive clinical and chest x-ray findings, first the patient should be treated with broad spectrum antibiotics to rule out other bacterial causes. If the patient doesn't respond, smear negative pulmonary TB can be strongly considered.

- **Mycobaterial culture** is the gold standard for making diagnosis. However the bacillus is slowly multiplying and it takes several weeks to grow the bacilli in a culture media. May be used for drug sensitivity tests.
- **Chest x-ray** presentations of tuberculosis are varied. Although any radiographic finding is possible, typically there will be nodular infiltrates and cavities in the upper lobe; pleural effusion is also common. Chest x-ray findings do not confirm diagnosis of TB.
- **Raised ESR** is a very important clue for the diagnosis even though this is nonspecific. There could also be anemia of chronic illness.
- **PPD skin** test is widely used to screen tuberculosis in developed countries where the prevalence of TB is low. Positive reactions are obtained when patients have the infection but do not have active disease or they have received BCG for immunization. Therefore, it is not a good method of screening in our country.

Standardized case Definition of Tuberculosis

After making diagnosis of TB proper case Definition should be made to decide on appropriate treatment. The definition of TB case depend on the following points

1. **Site of TB (Pulmonary Vs Extrapulmonary)**
   - **Pulmonary tuberculosis** (PTB) refers to disease involving the lung parenchyma. Therefore tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs.
   - **Extrapulmonary tuberculosis** (EPTB) refers to **tuberculosis** of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of **tuberculosis** chemotherapy. The case definition of an extrapulmonary TB case with several sites affected depends on the site representing the most severe form of disease.
2. **Bacteriology (result of sputum smear) : Smear positive Vs Smear negative**

   Identification of smear-positive cases is important, because they are the most infectious cases and usually have higher mortality;
   - **Pulmonary tuberculosis, sputum smear-positive (PTB+)**
     a) Two or more initial sputum smear examinations positive for AFB, or
     b) One sputum smear examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician, or
     c) One sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis.*
   - **Pulmonary tuberculosis, sputum smear-negative (PTB-)**

     Case of PTB that does not meet the above definition for smear-positive TB.

     This group includes cases without smear result, which should be exceptional in adults but are relatively more frequent in children.

Note. In keeping with good clinical and public health practice, diagnostic criteria for PTB-should include:

- A at least three sputum specimens negative for AFB, and
- A radiographic abnormalities consistent with active PTB, and
- No response to a course of broad-spectrum TB antibiotics, and
- Decision by a clinician to treat with a full course of ant tuberculosis chemotherapy.

- In health facilities where microscopy laboratory services are available and diagnostic criteria are properly applied, PTB smear-positive cases represent at least 65% of the total of PTB cases in adults, and 50% or more of all TB cases.
- Note that these proportions may be lower in high HIV-incidence populations.
- It is apparent from the above definitions that in the absence of culture, standard chest radiography is necessary to document cases of smear-negative PTB.

3. History of previous treatment of TB

In order to identify those patients at increased risk of acquired drug resistance and to prescribe appropriate treatment, a case should be defined according to whether or not the patient has previously received TB treatment.

The following definitions are used:

- **New:** a patient who has never had treatment for TB or who has taken ant tuberculosis drugs for less than 1 month.
- **Relapse:** a patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.
- **Treatment after failure:** a patient who is started on a re-treatment regimen after having failed previous treatment.
- **Treatment after default.** A patient who returns to treatment, positive bacteriologically, following interruption of treatment for 2 months or more.
- **Transfer in.** A patient who has been transferred from another TB register to continue **treatment**.
- **Other.** All cases that do not fit the above definitions. This group includes
  - **Chronic case,** a patient who is sputum-positive at the end of a re-treatment

4. Severity of the diseases

Bacillary load, extent of disease and anatomical site are considerations in determining TB disease severity and therefore the appropriate treatment. Involvement of an anatomical site results in classification as severe disease if there is a significant acute threat to life (e.g. pericardial TB), a risk of subsequent severe handicap (e.g. spinal TB), or both (e.g. meningeal TB).

Case definitions

- **Tuberculosis suspect.** Any person who presents with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks)

- **Case of tuberculosis.** A patient in whom TB has been bacteriologically confirmed or diagnosed by a clinician.
- **Definite case of tuberculosis:** a patient with positive culture for the *M.tuberculosis* complex.

Based on the above criteria and case definitions, a TB patient falls in to one of the four categories of treatment. This categorization helps in prioritizing patients and in selecting the type regime to be used in a patient.

Table I- 4 -1: Tuberculosis Treatment Category

TB treatment category	Patients	Recommended Treatment /Regimen
Category 1	• New smear positive PTB • Smear –ve PTB with extensive TB • Sever forms of extra pulmonary TB	**DOTs short course HRZE/S for 2 months + HR 4 MO or HE 6 MO Or H3R3 for 4 MO**
Category 2	• Relapse • Treatment Failure • Return after Default	**Retreatment 2HRZES/ 1HRZE + 5ERH**
Category 3	• Smear negative PTB with limited • EPTB less ever form • Children between 7 and 14 years old with any type of TB, who are not seriously ill	**2HRZ or 2H3R3E3 + HR 4 MO or HE 6 MO Or H3R3 for 4 MO**
Category 4	• Chromic cases	**2nd Line Anti TB drugs**

Anti Tuberculosis Chemotherapy

Aim of Treatment of Tuberculosis

- To cure the patient from the diseases and prevent death and complications
- To decrease transmission of Tuberculosis

Treatment of tuberculosis has two phases,

- **The intensive (initial) phase**: combination of 3 or more drugs is given for 2 months. In the retreatnment regimen it continued for 3 months. This is to decrease the bacterial load and make the patient non-infectious rapidly.
- **Continuation phase:** Two or three drugs used for 4 -5 months. This phase follows the intensive phase and the aim is to achieve complete cure.

♦ During the intensive phase of DOTS, the drugs must be collected daily and must be swallowed under the direct observation of a health worker. During the continuation phase, the drugs must be collected every month and self-administered by the patient.

♦ For category 2 pateints put on re-treatment, the whole duration of re-treatment, including the continuation phase, the drugs must be taken under the direct observation of a health worker. Streptomycin should not be included in the re-treatment for pregnant women.

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Table I- 4-2: Anti TB drugs are classified in to two groups

First Line Drugs (Essential Anti tuberculosis drugs): There are five drugs in use currently	**Second Line Drugs (reserve Anti TB drugs)** are used only in Chronic case of TB
• Streptomycin (S) in 1gm vial : the only drug given IM • Ethambutol (E) in 400mg tablet, • Isoniazeid (H) in 100mg and 300 mg tablet, • Rifampicin (R) in 150mg and 300mg tablets and • Pyrazinamide (Z) in 500mg tablets. **Fixed drug combinations** • RIF , INH , PZA(RHZ) 150/75/400mg • ETH and INH (EH) 400/150mg • RIF and INH (RH) 150/75mg • RIF, INH, PZA, ETB (RHZE) 150/75/400/225	• **AMINOGLYCOSIDES** ▸ Kanamycin and Amikacin ▸ Capreomycin (polypeptide) • **THIOAMIDES** ▸ Ethionamide ▸ Protionamide • **FLUOROQUINOLONES** ▸ Ofloxacin ▸ Ciprofloxacin • **CYCLOSERINE (AND TERIZIDONE)** • **P-AMINOSALICYCLIC ACID**

Side Efects of common Anti TB Drugs: Anti-tuberculosis drugs cause different side effects. These may be Minor where the drugs are continued or Major in which case the drugs should be discontinued and the patient referred

Table I-4-3: Side Effects of common Anti TB drugs and Treatment of side effects

Anti TB Drug	Severity of the adverse effect	Side Effects	Treatment of Side Effects
Isoniazide	**Minor**	Burning Sensation in the Feet (Peripheral neuropathy)	Pyridoxine 100 mg PO daily
	Major	Jaundice /Hepatitis	Stop INH
Rifampicine	**Minor**	Orange or red discoloration of urine Nausea , abdominal pain	Reassurance Take drug with small meal
	Major	Hepatitis , Acute renal failure shock , purpura	Stop Rifampcin
Ethambutol	**Minor**	None	
	Major	Optic neuritis : Visual impairment	Stop Ethambutol
Streptomycine	**Minor**	Mild skin rash Perioral parasthesia	Symptomatic treatment
	Major	Ototoxicity : Vertigo and hearing impairment	Stop Streptomycin
Pyrazinamide	**Minor**	Joint pain	Analgesics like Aspirin
	Major	Hepatotoxicity / jaundice	Stop Pyrazinamide

Important points to consider in the treatment of tuberculosis:

- Streptomycin should not be given to pregnant woman, and patients with renal failure and ear problems. It should be replaced by Ethambutol. Streptomycin dose should not be more than 750mg if the patient's age is > 50 years.
- Children who are 6 years or below should not be given Ethambutol because of damage to the eyes and children may not complain of it.
- Patients should be strictly followed after initiation of the drugs.

- All sputum-positive patients on DOTS must have one sputum specimen examined at the end of the 2nd, 5th and 7th month. If sputum is negative at the end of 8 weeks, the continuation phase can be started.
- Corticosteroids are added to the anti-TB in TB meningitis, pericarditis, and spinal TB. Adrenal TB patients should have replacement therapy.

Tuberculosis and HIV is dealt on HIV section

Refernces:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Tuberculosis, pages 953-965.
2) National TB Treatmnet guidline for Ethiopia
3) Treatment of Tuberculosis : Guidline for National programmes , Third edition , WHO- Geneva 2003
4) TB/HIV , a clinical manual , Second edition , WHO-Geneva , 2004

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5. Human Immuno Deficiency Virus – HIV/AIDS

Learning Objectives: At the end of the this Unit the student will be able to

1. *Define HIV disease and AIDS*
2. *Understand the basic virology of the etiologic agent*
3. *Describe the mode of transmission of HIV*
4. *Understand the epidemiology of HIV*
5. *Describe the pathophysiology of HIV/AIDS*
6. *Identify the clinical manifestations of HIV/AIDS*
7. *List the complications and Organ systems affected by HIV/AIDS*
8. *Describe the most commonly investigations for the diagnosis of HIV*
9. *Make an appropriate diagnosis of the common manifestations of HIV/AIDS and different opportunistic infections*
10. *Make appropriate WHO clinical staging of HIV/AIDS*
11. *Manage common opportunistic infections*
12. *Understand the basics of Antiretroviral drugs and HAART including indications /eligibility criteria for the initiation of ART*
13. *Initiate ART for most patients and follow patients on ART*
14. *Refer complicated cases of HIV/AIDS diseases to hospitals for better management*

Definition: HIV disease is a chronic infectious disease caused by the Human Immuno Deficiency Virus, which is characterized by spectrum starting from primary infection, with or without the acute syndrome, followed by a relatively long period of asymptomatic stage after which in most patient's progress to advanced and life threatening disease (AIDS)

Historical Back Ground

1981: AIDS was first recognized in USA among Homosexual males

PCP was seen among 5 homosexuals

Kaposi's sarcoma was diagnosed in 26 homosexuals with

1983: HIV virus was isolated from a patient with lymphadenopathy

1984: HIV virus was clearly demonstrated to be the causative agent for AIDS

Epidemiology

- According to UNAIDS report at the end of 2006 about 39.5 million people were living with HIV/AIDS, out of which 2.3 million were children and 17.7 million were women. In 2006 there were about 4.3 million new infections out of which 530, 000 were children < 15 years. There were about 2.9 million deaths out of which 380,000 were children.
- Sub-Saharan Africa is the worst affected by the pandemic with 25.7 million living with HIV, Out of which 2.1 million are children < 15 years. The overall adult prevalence in this region is 5.9 %. There were about 2.1 million deaths due to HIV/AIDS in 2006.
- Our country Ethiopia is the second most populous country in Sub-Saharan African suffering from the brunt of HIV/AIDS. In Ethiopia HIV was first detected in collected sera in 1984. The first two AIDS cases were reported to the Ministry of Health in1986.
- National HIV prevalence rate according to AIDS in Ethiopia 6ht report is 3.5% (the prevalence is different in Urban and Rural areas 10.1 % and 1.9 % respectively.) There are about 1.3 million people living with HIV/AIDS out of which 134,586 were children. There were nearly 128, 988 new infections in 2006 of which 12, 9196 are children. There were about 134, 450 deaths in 2006 among these 20,929 were children.

Mode of Transmission of HIV

1. Sexual Transmission:

- Is the major mode of transmission worldwide (90 %)
- The virus is found in high quantities in the sexual fluids (seminal and vaginal fluid) of people with HIV infection with in infected monocytes and in cell-free state
- Anal sex appears to be the sexual practice carrying the highest risk of transmitting HIV. The reasons being rectal mucosa is thin and fragile and there are susceptible cells (Langerhans cells) in the rectal mucosa
- Vaginal sex is also an effective from of transmission.
- The presence of other STDs like Syphilis , Gonorrhea etc increase the risk of acquiring or transmitting HIV infection by several fold, as the quantity of the virus in seminal or vaginal fluid significantly increase and the number of infected monocytes is high around the genital area in patients with STDs..
- Oral sex may have some risk however there are no reports so far attributable to oral sex.

2. ***Transmission through blood and blood products***
    - IV drug abusers who share needles and syringes have high risk .This is the main mode of transmission in Eastern Europe.
    - Blood or blood products transfusion from infected donors (the risk of infection is 90-100 %). Currently the risk is very minimal as blood and blood products are screened carefully using antibody and p24 antigen testing to identify donors in the widow period.
    - Transmission through sharp instruments, injection needles etc. There may be a risk of transmission from one patient to another or from an infected patient to health care provider
3. ***Mother to Child Transmission***
    - Without any intervention, the risk of mother to child transmission is 30-45% in the developing world and 15-30% in the developed world ,
    - HIV may be transmitted from infected mothers to children during
        i. Pregnancy:-10 % before the 3rd Trimester
        ii. Labor and Delivery:- 70 % late pregnancy and during labor
        iii. Breast Feeding :- 10-15 %
    - MTCT is by far the largest source of HIV infection in children under 15

Factors Influencing MTCT

Maternal Factors

- Maternal viral Load: The higher the viral load, the higher is the risk of MTCT
- Woman becomes infected with HIV during pregnancy
- Severe immune deficiency
- Clinical and immunological state
- Use of ART during pregnancy and postpartum to mother and newborn
- Viral, bacterial, and parasitic placental infection (especially malaria)
- Nutritional status, particularly vitamin A

Labor and Delivery

- Prolonged rupture of membranes (>4 hours)
- Acute chorioamnionitis
- Invasive fetal monitoring or delivery techniques

- Mixing of maternal and fetal body fluids
- Episiotomy
- First infant in a multiple birth

Fetal Conditions

- Premature delivery
- Immature immune status
- First-born twin

Infant Feeding Practices/Breastfeeding

- Mother becomes infected with HIV while breastfeeding (risk increases up to 20%)
- Mixed feeding (breast milk and other foods) increases risk
- Breast pathologies (lesions, infections)
- Advanced disease in the mother
- Poor maternal nutritional status
- Breastfeeding during the first 4–6 months
- The longer mother breastfeeds, the greater the risk

❖ HIV is not spread via non-sexual everyday casual contact between people like kissing, hugging and sharing common utensils, baths etc.

❖ HIV infected people are considered most infectious soon after acquiring the infection and during the AIDS (symptomatic) phase. However, remember that it is possible to transmit HIV any time during the disease.

Etiologic agent:

HIV is a retrovirus which belongs to the sub family of lente virus. HIV virus is cytopathic virus. There are 2 main Types of the virus

HIV- 1: is the most common cause of HIV Disease throughout the world and it has several groups and subtypes;

- **M group** which comprises 9 subtypes: A,B,C,D,F,G,H,J,K, as well as growing number of major circulating recombinant forms (CRFs) e.g. AE , AG etc
- **O group (outliers)**: relatively rare seen in Cameron and Gambia
- **N group: (reported only in Cameroon)**

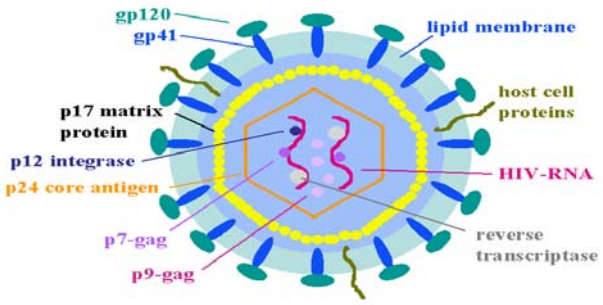
Global Pattern of HIV -1 distribution

- **Africa:** > 75 % of strains recovered to date have been subtypes A, C and D with C being the most common
- **Europe and Americas**: **s**ubtype B is the predominant strain

- **Asia:** recombinant forms such AE account of the infections in south East Asia while subtype C is prevalent in India. Subtype B is also seen in Asia.

HIV - 2: Was first identified in West Africa and it is mostly confined to West Africa, however a number of cases which can be traced to West Africa are found worldwide.

Morphology of the Virus



- HIV is Spherical shaped virus. The most important parts of the virus are:-
  - Its viral envelop has many small spikes which consists of two important glycopropteins gp41 and gp120 which play an important role when the virus attaches to its host cells
  - The viral capsid (core) which contains two single stranded viral RNA and an important enzyme for the virus called reverse transcriptase enzyme
  - The reverse transcriptase enzyme plays an important step in the life cycle of the virus. It converts the single stranded viral RNA into double stranded DNA (this process is called reverse transcription)

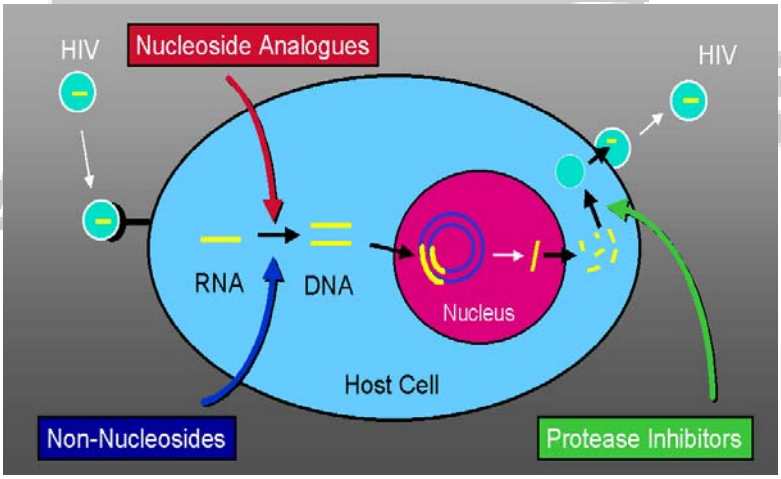
Characteristics of HIV

- HIV infect cells that express CD4 receptor molecules
- The CD_4 receptors are present on various types of blood cells including lymphocytes, macrophages, monocytes, tissue cells (e.g. Dendirtic cells in the genital tract and ano-rectal region) and glial cells of brain Successful entry of the virus to a target cell also requires cellular co-receptors
- A fusion co-receptor is designated CXCR5 for T-cell tropic stain and CCR4 for monocyte -macrophage tropic strains

- The receptor and co-receptors of CD4 cells interact with HIV's gp-120 and gp-41 proteins during entry into a cell

Life Cycle of HIV: Replication

1) ***Attachment /binding*** and fusion of the virus to the host cells
   - The receptor and co-receptors of CD4 cells interact with HIV's gp-120 and gp-41 proteins during entry into a cell
2) ***Uncoatting*** of the viral capsid and release of Viral RNA into the cytoplasm of the host cell
3) ***Reverse transcription:*** Viral RNA is concerted in to Double stranded DNA by reverse transcriptase enzyme
4) ***Translocation :*** viral DNA is Imported to cell nucleus
5) I***ntegration*** of proviral DNA to host-cell DNA
6) ***Cellular activation causes transcription*** (copying) of HIV DNA back to RNA
   - Some RNA translated to HIV proteins
   - Other RNA moved to cell membrane
7) ***Viral Assembly*** :HIV assembled under cell membrane and buddes from cell
8) ***Maturation :*** viral Proteases enzymes cleave longer proteins in to important viral proteins and help to convert immature viral particle into and infectious HIV



Life cycle of the virus and Sites of action for antiretroviral drugs

Pathogenesis:

CD_4 positive T-Lymphocytes (also known as T helper cells) play central role in the defense mechanism of the body against infection. They mainly coordinate the ***Cell mediated immune system*** and also assist the ***antibody mediated immune system***.

- HIV virus has special affinity to CD_4 T-cells and infects them
- HIV infection is characterized by a profound immunodeficiency from progressive decline of T-helper cells
- The pathogenetic mechanism of HIV disease is multi-factorial and multiphasic and it differs in different stage of the disease

Mechanism of CD_4 Cell Depletion

- HIV-mediated direct cytopathicity (single cell killing) – infected **CD_4** cells die
- HIV-mediated syncytia formation
- Defect in CD4 T-cell regeneration in relation to the rate of destruction
- Maintenance of homeostasis of total T-lymphocytes (decreased CD4, increased CD8)
- HIV-specific immune response (killing of virally infected and innocent cells)
- Auto-immune mechanism
- Programmed cell death (apoptosis)

Qualitative abnormalities (even the existing CD4 cells are dysfunctional)

- Impaired expression of IL-2
- Defective IL-2 and INF-Alfa production
- Decreased help to B-cells in production of immunogloblins

Peculiar Characteristics of HIV and reasons for Persistent Viremia

HIV is a unique infection in that, though the body reacts by producing antibodies to destroy the virus, the virus is not cleared, except partially in the early period of infection

A chronic infection is established, and it persists with varying degrees of viral replication. Viral replication is continuous in all stages (early infection, during the long period of clinical latency, and in advanced stage.) There is no virological latency.

Despite robust immune reaction, HIV evades elimination by the immune system and a chronic infection is established. Some of the mechanisms are:

- High level of viral mutation – HIV has an extraordinary ability to mutate
- Large pool of latently infected cells that cannot be eliminated by viral-specific CTLs
- Virus homes in lymphoid organs, while antibody is in the circulation
- Exhaustion of CD8 T-lymphocytes by excessive antigen stimulation
- HIV attacks CD-4 T-cells, which are central to both humeral and-cell mediated immunity
- HIV seeds itself in areas of the body where sufficient antibodies might not reach, e.g., the central nervous system

Progression of HIV is different in different individuals

Rapid progressors: After the initial infection patients progress fast and develop OIs and die within 2-3 years. Account for 15 % of all patients

Normal Progressors: After the initial primary infection patients remain health for 6- 8 years before they start having overt clinical manifestations: account for 80 % of all patients

Long term survivors: Patients who remain alive for 10-15 years after initial infection. In most the diseases might have progressed and there may be evidences of immunodeficiency.

Long term non progressors: This is individuals who have been infected with HIV for > 10 years. Their CD4 count may be in the normal range and they may remain clinically stable for several years

What affects disease progression in HIV Infected individuals

- **Viral set point:** The level of steady-state viremia (set-point) at six months to one year after infection, has an important prognostic implication for progression of HIV disease
    - Those with a high viral set-point have faster progression to AIDS, if not treated
- **Immune response**
    - High CD8 slow progression
    - Low CD8 rapid decline
- **Viral type**; HIV 2 slow course
- **Concomitant conditions**
    - Malnutrition hastens the progression of HIV

- Chronic infectious conditions e.g. Tuberculosis

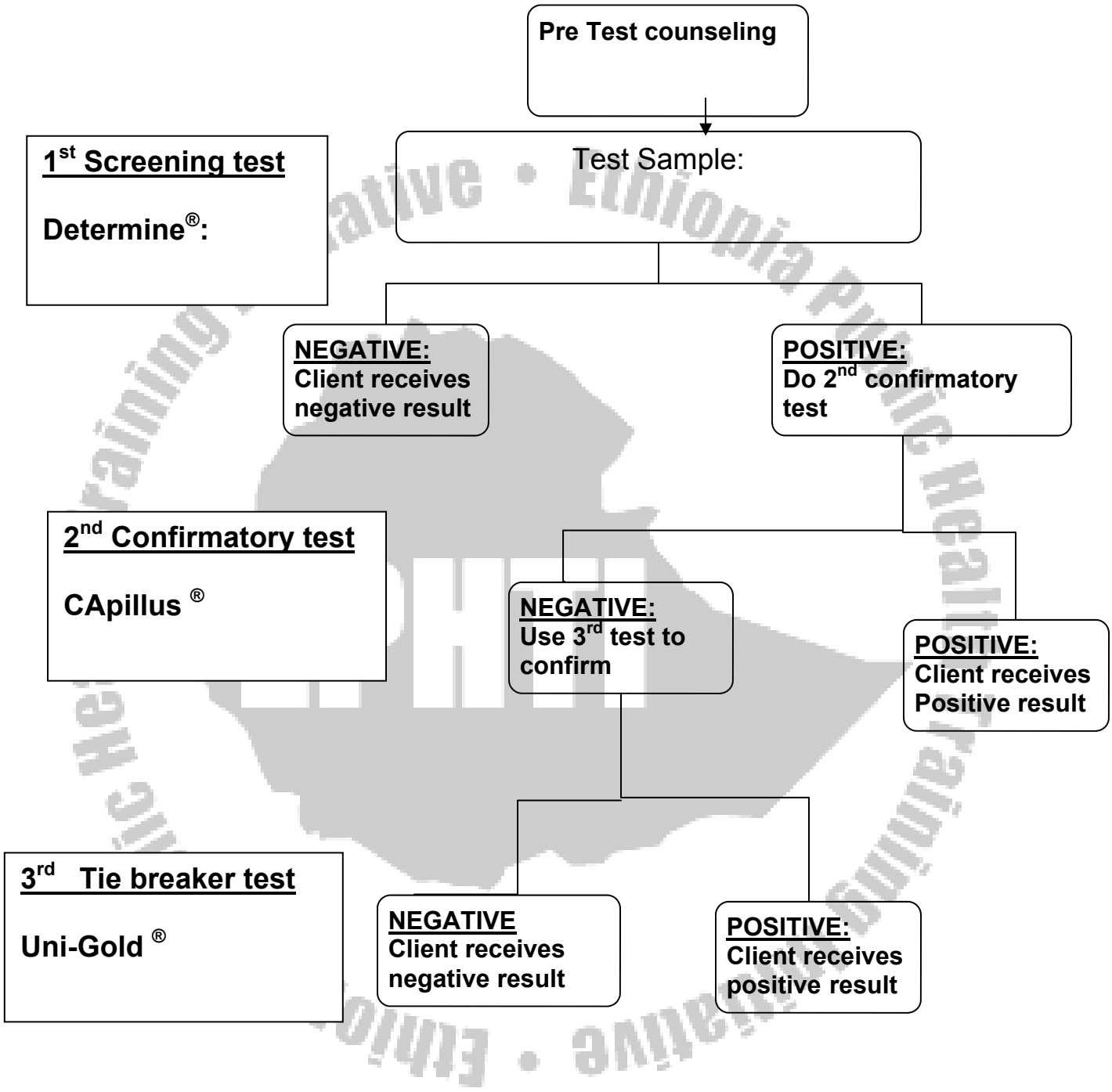
Diagnosis and Laboratory monitoring of HIV

1. **Serologic Tests :**
   a. **HIV antibody tests :-** detect antibodies formed by the immune system against HIV
      i. **ELISA : used to be standard screening test for HIV**
         - Tests for a number of antibody proteins in combination
         - A very *sensitive* test (. 99.5 %), but not very *specific*
         - A positive result needs to be confirmed by Western blot for confirmation
         - The test need skilled personnel , takes several hours
      ii. **Western blot: is an excellent confirmatory test.**
         - It has high specificity but relatively poor sensitivity
         - It should not be used for screening purpose
      iii. **Rapid HIV antibody testes**

      Advantages:
         - Rapid tests have reasonably good sensitivity and specificity (>99 %)
         - Easy logistically , does not need continuous water or electric supply
         - Can be done by less skilled personnel and the interpretation of results is easy
         - Test result can be made available in < 30 minutes

Because of these advantages of rapid tests WHO has recommend a serious of Rapid HIV antibody testes to be done to diagnose HIV infection.

Test Algorithm for HIV Diagnosis



- When the 1st test is non-reactive, then the client can receive negative HIV result
- When both tests are reactive, the final HIV result is positive.

- If one test is reactive and the other is non-reactive, then a third test known as a tiebreaker is performed.
- The tie-breaker determines the final result – if the tiebreaker is reactive, then the final HIV result is positive; if the tiebreaker is non-reactive, then the final HIV result is negative.

b. HIV antigen assays (Tests)

i. **P24 antigen capture assay:** this test detects p24 viral protein in the blood of HIV infected individuals. This viral protein can be detected during early infection, before seroconversion. Thus this test is used to detect blood donors during the Window period

2. DNA – PCR : Viral replication

- Is an extremely sensitive test -can detect 1-10 copies of HIV proviral DNA per ml of blood
- It uses PCR technology to amplify proviral DNA
- This test is costly and needs sophisticated instruments and highly skilled professional
- It is highly sensitive and the chance of false positivity is high. hence it should not be used for making initial diagnosis of HIV infection
- It is often used

i. To make early diagnosis of HIV in HIV exposed infants as serology tests are unable to diagnose HIV till the infant is 18 months old
ii. To diagnose or confirm virologic failure in patients who are not responding to ART
iii. When there is indeterminate serology

3. CD_4 T cell count : as CD4 cells play a crucial role in the body defense mechanism , measuring the amount of CD4 cells is an important indicator of the level of immune suppression that a patient infected with HIV has

- The average CD4 count of a normal person is in the range of 1000-1200 /$mm^{3.}$ Studies have shown the average CD4 count of normal Ethiopians is low
- In patients with HIV CD4 count drops by an average of 50 - 100 cells per year
- Tells you the level of immune damage inflicted by HIV

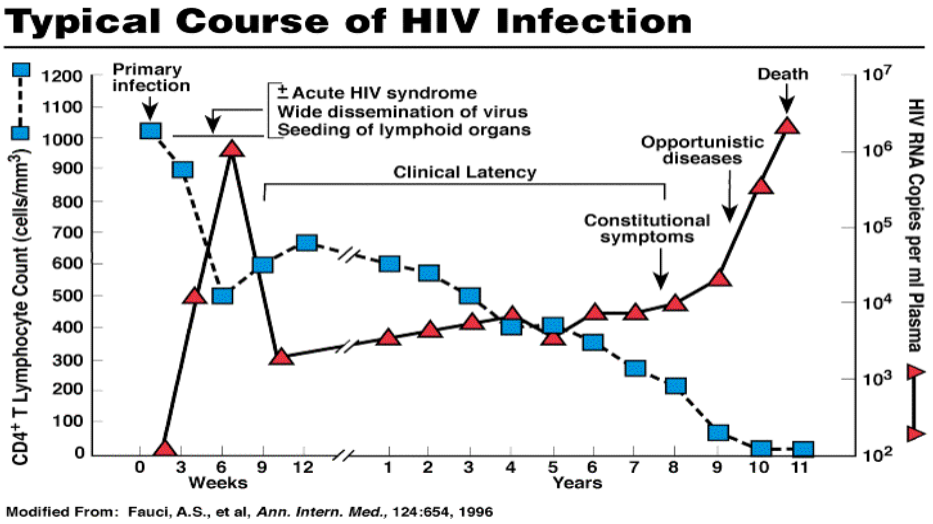
- It should never used to make diagnosis of HIV
- CD4 count may be variable depending on circumstances
    - Diurnal variation; High evening low at midnight
    - Inter current infection, use of steroids and stress could affect CD4 count
- Following the trend in CD4 count is us full in clinical decision making
- Percentage of CD4 count is useful in children below 6 years
- Importance's of CD4 count
    - To decide eligibility of a patient for ART
    - To follow the progress of a patient on ART
    - To diagnose immunologic failure in patients who are not responding well to ART

4. **Additional tests** that should be done is patients with HIV infection include:
    - HBV , HCV
    - FBP and ESR
    - SGOT/AST and SGPT/ALT
    - Serum Creatinine
    - Syphilis serology: RPR
    - AFB chest X-Ray where possible
    - Stool examination for parasites
    - Malaria blood slide
    - Pregnancy test for women in child bearing age

Natural History and Clinical Manifestations of HIV infection

The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease

1. ***Primary HIV Infection : Acute HIV syndrome and Seroconversion***
2. ***Asymptomatic stage – Clinical latency***
3. ***Early Symptomatic Diseases – mild immunodeficiency***
4. ***AIDS defining illnesses : Advanced immunodeficiency***



1. ***Primary HIV Infection : Acute HIV syndrome and Seroconversion***

   Acute HIV syndrome:

   - Some patients are asymptomatic but 50 – 70% of HIV infected individuals experience an acute clinical syndrome 3 – 6 weeks after primary infection
   - A flue like syndrome in which symptoms persist from 1 –several weeks and gradually subside
   - The typical clinical features includes
     - Fever
     - Pharyngitis, lymphadenopathy,
     - Headache, artheralgia, myalgia, malaise,
     - GI symptoms : Anorexia, nausea vomiting, diarrhea,
     - Erythematous maculopapular rash and mucocutaneous ulceration
     - Neurological symptoms: HIV in CSF, aseptic meningoencephalitis Encehphalitis, peripheral neuropathy

Most patients (> 90%) recover spontaneously 10 % manifest a fulminate course of immunologic and clinical deterioration

2. ***Asymptomatic stage – Clinical latency***

   - In most (90) of patients, primary infection with or without the acute syndrome is followed by a prolonged period of clinical latency

- The length of time from initial infection to the development of clinical disease varies greatly (median is 7-10 years.)
- Viral replication continues during this period of clinical latency. So there is no virologic latency
- The rate of disease progression is directly correlated with HIV RNA levels. Patients with high levels of HIV RNA progress to symptomatic disease faster than do patients with low levels of HIV RNA
- The CD_4 cell count fall progressively during this stage at an average rate of 50 cells/μl/year,

3. Early Symptomatic Diseases – mild immunodeficiency

- Patients begin to develop sign and symptoms of clinical illness , when CD_4 cell count falls below 500/μl,
- Most of the manifestations are due to minor opportunistic infections (not AIDS defining illnesses) or direct effect of long standing HIV

The clinical findings include:

a) Generalized lymphadenopathy

- Definition: enlarged lymph nodes (> 1cm) in ≥ 2 extra-inguinal sites for more than 3 months without an obvious cause.
- It is often the earliest symptom of HIV infection after primary infection

b) Oral lesions:

- Are usually indicative of fairly advanced immunologic decline, generally occurring in patients with CD4 count < 300 /μl.

i. Oral thrush:

- Appears as a white, cheesy exudates, often on an erythematous mucosa (most commonly seen on the soft palate) which gives an erythematous or bleeding surface on scraping
- When it involves the esophagus, patients complain of difficulty and/or pain on swallowing
- Is due to Candida infection
- Confirmatory diagnosis is by direct examination of a scraping for pseudohyphal elements
- **Treatment** - Apply 0.25% Gential Violet BID and/or
  Nystatin tablets or suspension 500,000 IU every 6 hr

If pharynx or esophagus involved; Ketoconazole 200 mg PO BID for 2 weeks or Miconazole oral gel.

ii. Oral hairy leukoplakia:

- Appears as a filamentous white lesion, generally along the lateral borders of the tongue.
- Is presumed due to Epstein – Barr virus infection

iii. Apthous ulcer:

- Ulcer on the oral cavity or pharynx of unknown etiology
- Usually are painful and may interfere in swallowing

c) Herpes zoster (shingles)

- Seen in 10 – 20% of patients with HIV infection
- It is a reactivation syndrome of varicella zoster virus
- Indicates a modest decline in immune function and is often the first clinical indication of immunodeficiency
- Lesions are usually localized to a single dermatome, but may extend over several dermatomes and frank cutaneous dissemination may be seen.
- It has a relapse rate of 20%

d) Thrombocytopenia:

- Thrombocytopenia in HIV infection has immunologic base (is due to auto immune destruction of platlets).
- It is very similar to IPT (idiopathic thrombocytopenic purpura)
- Since most patients have platelet count of >50,000/μl serious clinical problem are seen rarely.
- In some patients, when the platelet count falls < 10,000/μl, clinical symptoms such as bleeding of the gums, extremity petechiae, and easy bruisability are common presenting features.
- Bone marrow examination is normal or may show increased megakaryocytes

e) Other clinical conditions seen in patients during early stage of HIV:

- Molluscum contagiosum
- Recurrent bouts of oral or genital herpes simplex
- Condylomata accuminata.

HIV/AIDS associated illnesses affecting different Organ Functions

Opportunistic infections: are infections that develop as a result of HIV−inflicted damage to the immune system.

- OIs are leading causes of morbidity and mortality in HIV-infected persons
- Most of the common OIs are preventable as well as treatable
- In resource-limited settings, it may be difficult to diagnose and manage OIs
- Most opportunistic infections and complications of HIV develop when the CD4 count drops below 200cells /ml

Opportunistic malignancies: are neaoplastic conditions which tend to occur more frequently in patients with underlining immunodeficiency.

Disease of the Respiratory system associated with HIV infection

- The Respiratory system is the most common site of HIV-associated complications/illnesses.
- Respiratory problems are the leading cause of morbidity & mortality in persons infected with HIV.
- Many of the respiratory problems are both Preventable & Treatable.
- Therefore, Prevention, evaluation, and treatment of pulmonary disease is an essential part of managing patients with HIV infection

There is a wide spectrum of Pulmonary Manifestations.

Opportunistic Infection

- Bacterial: Streptococal, H.infleunza, gram negatives , Staphylococcal
- Mycobacterial: M. tuberculosis, M. kansasi, M. aveum intracellularie
- Fungal: PCP, Cryptococcus neofrmans, Histoplasmosis, Coccidiodeoco mycosis, Aspergillosis
- Viral: Cutomegaovirus, Herpes simplex infection
- Parasitic pathogens: Toxoplasmosis, Strongliodosis

Opportunistic Malignancies

- Pulmonary Kaposi's sarcoma
- Non Hodgkin's Lymphoma

- The type of OIs or OMs that a patient develops depend on the degree of immunosupression i.e. each of the OIs and OMs typically develop at or

below a characteristic CD4 cell count range. Therefore CD4 cell count is an excellent indicator of the risk of developing a specific OI or OM.

- Knowing the stage of the disease will be useful in limiting the differential diagnosis.
- In the advanced stage of HIV infection, a person may be infected by more than one pathogen.

Respiratory manifestations which may occur at any CD4 level

- Upper respiratory tract infection (URI) :Sinusitis , Pharyngitis
- Acute bronchitis
- Bacterial pneumonia
- Tuberculosis
- Non-Hodgkin's lymphoma

Respiratory manifestations which may occur when CD4 level is <500/mm^3

- Bacterial Pneumonia
- Pulmonary TB

Respiratory manifestations which may occur when CD4 level is <200/ mm^3

- Pneumocystis carinii pneumonia
- Cryptococcus neoformans pneumonia
- Bacterial pneumonia (associated with bacteremia/sepsis)
- Disseminated or extrapulmonary tuberculosis

Respiratory manifestations which may occur when CD4 level is <100/ mm^3

- Pulmonary Kaposi's sarcoma
- Bacterial pneumonia (Gram-negative bacilli and Staphylococcus aureus increased)
- Toxoplasma pneumonitis

Respiratory manifestations which may occur when CD4 level is <50/ mm^3

- Disseminated Histoplasma capsulatum
- Disseminated Coccidioides immitis
- Cytomegalovirus pneumonitis
- Disseminated Mycobacterium avium complex
- Disseminated mycobacterium (nontuberculous)
- Aspergillus species pneumonia

Knowledge of the relative frequencies of these pulmonary diseases is IMPORTANT.

Bacterial Pneumonia

- Common etiological agents: *S. pneumoniae*
- As the degree of immunosuppressioin worsens pneumonia may be recurrent and associated with sepsis
- Clinical presentation: Abrupt onset with fever, cough, production of purulent sputum, dyspnea, and pleuritic chest pain
- Recommended Investigations : Chest X-ray, blood culture, FBC, gram stain of sputum, sputum culture and sensitivity
- Common findings: X-ray may show pneumonic consolidation, infiltrates, or pleural effusion; leukocytosis; blood cultures may be positive
- **Treatment:**

  Antibiotics: Penicillin (procaine Pen/Crystalinne Pen), Amoxicillin fluoroquiolones

  Supplemental Oxygen

Pneumocystis carinii Pneumonia (P. jiroveci pneumonia)

Etiologic agent: *P. jiroveci* is fungus which is the etiologic agent for PCP

Epidemiology

- One of the commonest OIs in industrialized countries. However the incidence has declined over the years due to HAART and use of CPT Prophylaxis
- Used to be considered rare in Africa (Early studies in 1990s showed 4-15% prevalence , however recent studies show a prevalence of 25-52%
- In Ethiopia: though PCP is commonly seen in clinical practice there is only limited published information. Study done by *G. Aderaye (et al AIDS 2003, 17: 435-440)* shows 30.3% prevalence of P. carinii among expectorated sputum samples of HIV+/PTB- Pts. This suggests that PCP may be an important differential diagnosis amongst HIV + patients
- 50% of patients experience at least one bout of PCP during the course of their Life time.
- Transmitted from human to human, or from environmental reservoirs to human

Clinical Presentation

- Mode of presentation- PCP has indolent course characterized by weeks of vague symptoms prior to presentation or diagnosis. Median duration of symptom is 28 days.
- Dyspnea and fever are cardinal symptoms
- Cough with scanty sputum in > 2/3 of cases

Signs: Findings on physical examination are minimal, and the usual findings for pneumonia may not be noted.

- Respiratory distress ± Cyanosis
- Little abnormality on chest examination rhonchi or wheeze may be heard, especially in patients with some other underlying pulmonary disease, findings of consolidation are usually absent.
- P. carinii appears to be capable of hematogenic spread and seeding a variety of organ systems as well as causing a primary infection of the ear.

Diagnostic Work-up

1) **Chest x-ray is helpful**
   Could be normal. Diffuse bilateral alveolar/interstitial infiltrates is the usual findings
2) **LDH is elevated in > 90% of cases**: Has a very high negative predictive value i.e. if LDH level is low in a patient the diagnosis of PCP is less likely
3) **Definitive Dx** –demonstration of the trophozoite or cyst from the organisms in samples obtained from Induced sputum in which the yield is 60% or Brocho-alveolar lavage in which the yield is 95% . Staining: Wright-Giemsa, Methenamine silver, Direct IF, nPCR
4) **Other tests: Gallium 67 Scan, PFT, ABG**

Management (Treatment)

1) **Antibiotics :**
   - The gold standard for therapy of PCP at present is co-trimoxazole IV/PO
   - It is effective in > 90% of patients.
   - Usual dose, 15 mg/kg/day (trimethoprim) in 3-4 divided doses (3-4 480 mg tabs 4X/day)
   - Duration of Rx - 21 days (3 weeks)

- The major disadvantage is the relatively high incidence of side effects rash, fever, leucopenia 10% (HIV -ve) Vs 50% (HIV +ve)
- Response to treatment may not occur until the end of first week and the patient may get worse during the first few days owing to the inflammatory response resulting from the death of large number of organisms in the lungs.

♦ **Alternative Regimens**:

- Clindamycin 600 mg IV q8h or 300-400 mg PO q6h + primaquine 15-30 mg base/day x 21 days
- Pentamidine 4mg/kg/day IVX21 days
- Atovaquone 750 mg PO bid with meal x 21 days

2) **Adjuvant Treatment:**

- ***Supplemental O_2***
- ***Steroids:*** reduces mortality by 50% and the need for mechanical ventilation. Steroids reduce the inflammatory response and its adverse clinical consequences.

  Start within 72 hours of presentation

  ♦ Indications are if the patient is in:

  - Moderate / severe respiratory distress or cyanotic
  - Pa O_2 < 70mmHg

Dose: Prednisone 40 mg PO bid x 5 days

40 mg daily for 5 days

20 mg daily for 11 days

PCP - preventive therapies

Primary Prophylaxis is strongly recommended for HIV infected person with evidence of significant immune deficiency:

♦ CD4+ count < 200/µl (CD_4 cell percentage of less than 15% in children)

♦ HIV associated thrush

♦ Unexplained fever

Secondary prophylaxis is indicated for patients with prior episode of PCP

PCP - preventive therapies drugs/regimens:

- TMP-SMX two tablets/day (single strength)
- TMP-SMX two tablets three times per week

Alternative regimens:

- Dapsone 100 mg PO daily
- Dapsone 50 mg PO daily, plus pyrimethamine 50 mg PO weekly, plus leucovirin25 mg Po weekly
- Aerosolized Pentamidine 300 mg monthly via nebulizer
- Atovaqoune 1500 mg daily

N.B. The prevention of PCP may also be beneficial in reducing the risk of having other HIV associated infections such as CNS toxoplasmosis and other bacterial infections.

HIV and Tuberculosis

TB is the leading OI in developing countries

Impact of HIV on tuberculosis

HIV affects almost all aspects of TB.

Effect of HIV on Epidemiology of TB

- Increases incidence and prevalence of TB .Life time risk of developing TB is 50%among HIV positives compared to 5-10% in HIV negative patients
- HIV is the most potent factor known to increase risk of progression from *M. tuberculosis* infection to active disease.
- The seroprevalence of HIV among TB patients may range from 30 % - 60 %

Effect of HIV Clinical Manifestations of TB and it Diagnosis:

Clinical Presentation depends on degree of immunosupression

Table I-5-1. Manifestaions of Tunerculosis in early and advanced HIV

	Early stage of HIV Infection **:when CD_4 count >200 cells/mm^3**	***Late stage of HIV Infection*** **when CD_4 count <200 cells/mm^3**
Clinical Presentation	Similar to non HIV infected with productive cough Pulmonary manifestations dominate	**Atypical presentation :** Extrapulmonary TB is more common TB tends to be disseminated (involving different organs like meningitis, pleura, pericardium, Lymph nodes etc)
Laboratory Diagnosis ***Sputum smear***	*Often positive*	*Often negative*
PPD	*Often reactive with >10mm*	*Often negative or annergic*
Chest X-ray In the setting of an HIV epidemic, it is no longer possible to look at a CXR and say that it is TB or it is not TB!	Typical CXR findings of TB Upper lobe and or bilateral infiltrates Cavitations Pulmonary fibrosis	Atypical CXR findings CXR may show interstitial infiltrates especially in lower zones with no features of cavitation and fibrosis Negative CXR can be associated with sputum AFB+ (12% with pulmonary disease) In the setting of an HIV epidemic, it is no longer possible to look at a CXR and say that it is TB or it is not TB!

Treatment of TB in HIV infected patients

- When TB and HIV are coexisting TB is more life threatening and it should be treated first and patients should be stabilized
- The same Combination anti-TB drugs are given based on the treatment category

- Close follow-up of patients on DOTs is required
- Complete cure from TB may be achieved in six to eight months

Most patients who have TB-HIV co infection are eligible for ART

When to start ART in patients on Anti Tb Medication depends on CD4 count and the clinical condition of the patient

- CD4 < 50 /$mm^{3:}$ start ART as soon as the patient tolerates the Anti Tb medication
- CD4 count between 50 – 200 mm^3 start anti TB after completion of intensive phase of DOTs
- CD4 > 200 mm^3 ART can be initiated after compilation of Anti-TB treatment

Challenges / Problems in treatment of TB/HIV co infected patients

- Increased morbidity, mortality and high case fatality rate
- Increased drug toxicity
- Decreased Drug absorption
- High pill burden which may decrease adherence to treatment
- Drug Interaction between Anti TB drugs and ARTs

Impact of TB on HIV

- TB hastens the rate of HIV progression.
- Tuberculosis is the leading cause of illness and death among PLWHAs.

INH Preventive Therapy

- Rationale: Life time risk of having active TB in patients with HIV is 50% with Annual risk of 7 - 9% (compared to only 5-10 % life time risk in non HIV infected)
- It is advisable to give INH prophylaxis for HIV infected patents
- Patients should be screening for active TB before they are given preventive therapy

Treatment

- INH 300mg/d for 6-9 months.
  - Alternatively, Rifampicin for 4 months can be used

Neurological Manifestations of HIV/AIDS

- The nervous system is the second commonly affected organ system by HIV next to the respiratory system
- Common cause of Morbidity & Mortality
- Occur at any stage of HIV infection
- All levels of the neuro-axis are involved
- Clinical manifestations are variable

Pathogenetic Mechanisms for Neurologic manifestations

1. Directly related to HIV

- Aseptic Meningitis
- AIDS dementia complex
- Myelopathy
- Peripheral Neuropathy: AIDP(Acute demylinating distal polyneuropathy), MNM (mononuritis multiplex), DSPN (distal sensory ply neuropathy)
- Myopathy
- Vasculitis

2. Secondary to Immunodeficiency

A. Opportunistic Infections

- CNS Toxoplasmosis
- Cryptococcal Meningitis
- Tuberculos Meningitis/Tuberculoma
- PML
- Neuro-syphilis
- CMV polyradiculopathy/Encephalitis

B. Opportunistic Malignancies

- Primary CNS Lymphoma

3. ART related

- Peripheral Neuropathy :d4T, DDI
- Myopathy :ZDV
- EFV related – Psychiatric Manifestations

Epidemiology

High incidence of neurological disease among HIV patients:

- 7-20% of initial AIDS diagnoses,
- 30-70% prevalence among inpatients
- >90% in post mortem studies

Aseptic meningitis:

- It may occur at any time in the course of HIV infection, most commonly at the time of acute HIV infection. However it becomes increasingly rare following the development of AIDS.
- Patients experience a syndrome of headache, photophobia, sometimes frank-encephalitis and cranial nerve involvement, (commonly VII cranial nerve is affected)

CSF findings - lymphocyte pleocytosis 10-100 cells/µl

- Increased protein level protein< 100mg/dl,
- Normal glucose level

The syndrome usually resolves spontaneously within 2-4 weeks.

Diagnosis of HIV: HIV serology may be negative if it occurs during the primary HIV infection. To confirm the diagnosis of HIV p24 atg or DNA PCR may be done or Repeat HIV serology after few weeks

CNS TOXOPLASMOSIS

Etiology: ***Toxoplasmosis is caused by protozoa, Toxoplasma gondii***

Epidemiology

- Zoonotic infection cats are the definite hosts and excrete the oocysts in their feces and can be transmitted from animals to humans.
- T. gondii cysts are also found in under-cooked meat.
- Prevalence of latent Toxoplasma infection in the general population is high - 80% in Ethiopia
- Toxoplasmosis gondii is the most common cause of secondary CNS infection in patients with AIDS.

- It is generally a late complication of HIV infection and usually occurs when the CD_4 cell count is less than 100/mm^3.
- It is thought to represent a reactivation syndrome of prior infection.

Clinical Features

- Onset - Subacute
- Fever, Headache, Hemiparesis, Seizures and altered mentation
- Over 90% present with Focal neurologic deficits
- 10% of patients present with encephalitis picture – confusion or comma and become more toxic
- Commonly affected areas – Basal ganglia, brain stem and cerebellum
- Extra-cranial manifestation:
  - Retinitis
  - Myocarditis
  - Pneumonitis (lung)

Diagnosis

Clinical (Hx + P/E) + Neuro-imaging + Therapeutic Trial +/--Histology - Biopsy

Neuroimaging (CT/MRI):

- Multiple ring enhancing lesions are the findings in most patients (90%) with mass effect and edema
- Preferential location: basal ganglia, grey-white junction, white matter

Serologic assays: Limited value, a negative toxoplasma antibody test makes the diagnosis less likely

Histology: brain biopsy – In patients with treatment failure (not possible in our country)

Treatment

Regimen 1

Loading dose of pyrimethamine 50-75mg/day for 2-3 days, followed by

Pyrimethamine 25-50 mg/day, plus sulfadiazine 2 - 4 gm/d in divided doses, PO, plus folinic acid 10-20mg/d

Regimen 2

Pyrimethamine and leucovorin plus clindamycin 450 mg q8hrs

Duration of Rx: 6 weeks, or 3 weeks after complete resolution of lesions on CT

Continue suppressive Rx for life: pyrimethamine 25mg/day + sulfadiazine2g/day + folinic acid 5-10mg/day

High rate of adverse reactions

Regimen 3

Fansidar PLUS Folinic Acid (Pyrimethamine 25 mg +Sulfadoxin 500mg)

N.B. As the other preparations are not available in Ethiopia, Fansidar is a drug which is widely used

Dose: Fansidar 525 mg tabs 2 tabs PO BID for 2 days and then 1 tab PO/day

If the patient is very critical, add Doxycycline 100mg PO BID

Side effects:

- Leukopenia is the main side effect of the treatment. A higher dose of fansidar (2 tab/day) has been found to be associated with frequent incidence of fatal hemorrhage.
- Check for bleeding tendency such as gum bleeding, epistaxis, hematuria
- Do Hgb, WBC and platelet count once per week.
- To prevent these side effects, give folinic 10mg PO per day or advice to take cream cake daily.
- If there is bleeding tendency, stop Fansider and start Doxycycline 100mg PO BID.
- ***Alternatives:***

  Co-trimoxazole, or Clindamycin+Pyrimethamine/Primaquine,
- Azithromycin,Clarithromycin,

  Doxycycline

Indication for Steroids and dose :

- Evidence of marked increase in Intra cranial pressure and altered mentation
- Dose : administer Dexamethasone 8 mg IV stat and then 4 mg IV QID till the

Suppressive/Maintenance therapy: Fansidar 1 tab per day should be continued.

- Suppressive therapy (secondary prophylaxis) can be stopped when the CD4 count is more than 200 for 6 months

Preventive Therapy

Indications:

CD4+ count < 100cells/μl

Regimens

TMP-SMX two tablets per day

TMP-SMX two tablets 3 times per week

Alternative Regimens

Dapsone plus Pyrimethamine plus leucovirin

N.B. Primary prophylaxis can be stopped if CD4 count >200cells/ml for more than three months following HAART

Cryptococcal Meningitis

Etiology: *Cryptococcus neoformans, which is yeast*- like fungus.

Pigeon droppings commonly contain serotypes A or D

Infection is acquired through inhalation

Epidemiology:

- Is the leading cause of meningitis in patients with AIDS
- Is the initial AIDS defining illness in 2 % of patients
- Particularly common in patients with AIDS is Africa

Clinical Features

- Occurs late in the course of HIV/AIDS – when CD4 count is, 100/mm^3
- CNS and meningial involvement is seen in 67-85 % of patients
- Low grade fever n nausea , vomiting , headache ,
- Both fever and nuchal rigidity are often mild or lacking
- Papilledema is seen in one third of patients
- Neck stiffness , Photophobia – Meningial signs are seen in 30% of patients
- Late manifestations : Confusion , altered state of consciousness → comma

Other organ systems affected

- ***Extra cranial manifestations***: Occasionally appears as pulmonary or disseminated disease that includes the skin (10%).
- Cutaneous Cryptococcosis: centrally umblicated multiple lesions on the face (look very much like Molluscum contagiosum.)
- Pulmonary disease
- Fungemia
- Lymphadenopathy
- The prostate gland may be a reservoirs for smoldering infection

Diagnosis

LP – CSF Analysis

- Opening pressure is high
- WBC with differential, Protein, Glucose is normal in 1/3 of patients
- Indian Ink – Positive in 60-80%
- CSF Cryptococcal Antigen – Positive in 95-99%
- Cryptococcal Culture – Gold Standard

Treatment

Induction

Amphotericin B (with or without flucytosine)

0. 7-1 mg/kg for two to three weeks followed by consolidation.

Consolidation

Fluconazole 400 mg, PO, daily for 8-10wks OR until CSF is sterile

Maintenance :(suppressive)

Fluconazole, 200 mg, PO, daily life long

Adjunct treatment

- **Management of raised intracranial pressure**;
  - If CSF opening pressure- CSF drainage until CSF pressure is < 200 mm H2O; repeat LP daily until stable OR CSF pressure normalizes
- There is no place for Dexamethsone
- Discontinue maintenance or secondary prophylaxis when CD4 count rises to > 200 /mm3 for more than 6 months after completion of treatment following in patients who are taking HAART

Progressive Multifocal Leukoencephalopathy (PML)

Epidemiology of PML

- Reactivation of JC Virus It is seen in 2-4% of AIDS Pts

Clinical presentation

- Occurs late in the course of HIV when the CD4 counts< 100/µl
- Subacute onset
- The patient is afebrile, alert no headache
- Multifocal neurologic deficit
- Variable presentation: “Classic triad’: dementia, hemiparesis, and hemianopsia.

- Serology: 90% adults are seropositive for JC virus

Diagnosis - PML

- CSF is often non-diagnostic , JCV PCR or brain biopsy may help to make diagnosis c

PML Treatment

No effective treatment. But initiation of HAART increases survival to

Primary CNS Lymphoma

Clinical Presentation

Occurs late in the course of HIV when the CD4+ counts: < 100/µl

Occurs in 2-4% of AIDS patients

Symptoms and signs

- Confusion, lethargy, memory loss; 57%
- Hemiparesis or aphasia 40%
- Seizures 14%
- Cranial nerve palsy 9%
- Headaches only 3%
- **No fever** unless concomitant infection

Neuroimaging

- CT/MRI: multiple lesions as frequent as single lesion. (Irregular and solid enhancement, subependymal enhancement more specific, variable mass effect. Localization mainly periventricular

CSF : Epstein-barr virus DNA PCR – CSF (sensitivity: 85-100% ,specificity: 98-100%)

Histology: Diffusely infiltrating, multicentric tumor of B cell lineage with the presence of EBV genome in ~100%

Treatment

- Cytotoxic chemotherapy is not effective
- Radiotherapy can help some patients
- Response to steroids variable

HIV- associated Dementia Complex /HIV encephalopathy /*HIV-1 associated Dementia Complex*

- First AIDS defining illness in up to 5-10%
- Major cause of dementia in young people

- A major feature of this entity is the development of dementia, which is defined as a decline in cognitive ability from a previous level.
- TRIAD : cognitive, motor and behavioral dysfunction

Table I-5-2. Stages of ADIS dementia complex

	Cognition	**Behavior**	**Motor**
Early	Inability to Concentrate	Altered personality	
Middle	Mental Slowing Forgetfulness	Social withdrawal	Poor coordination
Late	Global dementia	Apathy	Paraparesis

Diagnosis*:*

- Neuropsychological tests
- Mini-mental test
- It is often a diagnosis of Exclusion

Treatment:

- HAART – most patients improve with HAART with possible benefit from ARV agents that penetrate the CNS (AZT, d4T, ABC, Nevarpine)
- Supportive care

Peripheral Neuropathies

Occurs in 1/3 of pts with AIDS

Type:

- Mono neuropathy e.g. Bell's palsy
- Mononuritis multiplex
- Distal sensory peripheral polyneuropathy (DSPN)

DSPN: Is the most common.

- It may be cause by HIV infection or ART mainly d4T and DDI

- It presents with symmetric bilateral painful burning sensation parasthesia and tingling of the feet and lower extremities ,

Diagnosis: Clinical, Nerve conduction study, Exclusion of other causes

Treatment: Symptomatic treatment and discontinuation or changing the drug which is causing it when symptoms are sever,

Seizure

- Seizure is a relatively frequent complication of HIV infection.
- May be a consequence of opportunistic infections, neoplasms, or HIV encephalitis.
- The seizure threshold is often lower than normal in patients with HIV infection owing to the frequent presence of electrolyte abnormalities.
- It may be the presenting clinical symptom of HIV disease.

Common causes of Seizure in HIV patients

- CNS toxoplasmosis 15-40 % of patients
- Primary CNS lymphoma15-35% of patients
- Cryptococcal meningitis 8% of patients
- HIV encephalopathy 7-50 % of patients

Treatment

- Most of the time patients will have 2 or more seizures suggesting that anticonvulsant therapy is indicated in all patients with HIV infection and seizures, unless a rapidly correctable cause is found.
- While Phenytoin (100 mg PO TID) remains the initial treatment of choice, Phenobarbital (100mg PO every night) or Valproic acid are also alternatives.

Gastrointestinal diseases in patients infected with HIV

Candidiasis

Caused by *Candida albicans*

Oral Candidiasis

Oral thrush:

- Appears as a white, cheesy exudates, often on an erythematous mucosa (most commonly seen on the soft palate) which gives an erythematous or bleeding surface on scraping

- Erythematous Form : there is predominantly erythema rather that white patches

Esophageal Candidiasis

- Usually coincides with CD4 count of < 50 /µl
- Causes substantial pain or a sense of obstruction on swallowing
- Most lesions occur on the distal third of the esophagus and appear on endoscopy as redness, edema and focal white patches or ulcers
- If and HIV infected person has oral thrush and substernal pain up on swallowing presumed diagnosis of Esophageal Candidiasis can be made s
- Endoscopy would prove the diagnosis, but is unnecessary if the patient responds to antifungal therapy
- Linear ulcerations of the esophagus may be seen on barium x-ray.

Treatment

Oral candidiasis

- Nystatin IU/ml suspension 2.5-5 ml gargled 5X daily
- 2% Miconazole oral gel applied 2-3 x daily
- Amphotericin B lozenges
- Fluconazole 100mg –200mg PO /day for 7-14days in severe and persistent cases
- Oral hygiene, discontinue steroids and antibiotics if the patient is taking any

Esophageal Candidiasis

First line: Fluconazole 200mg/day PO (up to 400mg/day) for 14-21 days

Alternately

- Ketoconazole 200-400mg for 14-21 days
- Itraconazole 200mg/day for 14-21 days

Diarrhea in HIV positive patients

- Is a common clinical condition in HIV infected patients (>50%)
- May be acute or chronic , watery , mucoid or bloody
- May or may not be associated with fever
- Spectrum may depend on the degree of immunodeficiency state
- Pathogens may be: Bacterial, Viral, Protozoal, Fungal ,Spirochetal ,Mycobacterial ,Metazoal , Others (malignancies)

Mechanism of diarrhea

- Adhesion to mucosal surface
- Enterotoxin
- Entero-invasion
- Atrophy of mucosal surface

Chronic Diarrheas

Definition – Diarrhea lasting for more than two weeks with a single watery bowel motion and or three or more loose stools per day

- Diarrhea occurs in 30-90% HIV-positive cases in Europe and USA and in 90% of cases in the developing countries
- Frequency of diarrhea increases as the CD4 count falls
- With HAART, incidence of chronic diarrhea decreases

Protozoa that cause chronic Diarrhia in HIV patients:

- *Cryptosporidia*
- *Isospora belli*
- *Microsporidium*

HIV enteropathy: (AIDS enteropathy)

- Chronic diarrheal syndrome for which no etiologic agent other than HIV can be identified
- It is most likely a direct result of HIV infection

Clinical features

- Early stage : intermittent self limiting diarrhea however in advanced stage, persistent life threatening diarrhea
- Copious amount of stool several times per/day associated with abdominal cramp. nausea and vomiting may also be present
- Significant weight loss (wasting) may occur due to the associated malabsorption
- Fluid and electrolyte depletion

Diagnostic investigation

- Stool Microscopy
- Culture
- Intestinal biopsy
- Special stains: Modified AFB stain

Treatment

1. General treatment of chronic diarrhea

- Hydration: oral , parentaral with electrolyte replacement
- Symptomatic treatment : Anti-diarrheal agents
  - Loperamide 2-4 mg QID
  - Lomotil 5 mg QID
  - Tincture of opium 0.3 ml QID
  - Codeine tablets

2. Specific treatment

Cryptosporidium

- Nitazoxanide 0.5 – 1.0 gm bid or
- Paromomycin 1 gm bid + azithromycin 600 mg qd

Isospora

- Cotrimoxazole 2 tabs QID for x 10 d, then bid for 3 weeks OR Pyrimethamine 75 mg + folinic acid 10
- Chronic suppression (secondary prevention): Cotrimoxazole 2 tabs /day OR pyrimethamine 25 mg + folinic acid 5 mg qd

Problem: malabsorption of drugs

Strongyloidias

- Parasitic infection caused by Strongyliod stercolaris
- Acquired through skin penetration of its larva form
- Auto infection is common
- In its life cycle there is transition via the lungs and settles in the GI tract, primarily small intestine free-living or parasitic
- Usually a mild disease in immunocopetent individuals
- Disseminated infection common in immuno-compromised hosts,
- Systemic manifestation may mimic sepsis

Clinical Manifestation

- Asymptomatic to mild symptoms in immuno-competent individuals with occasional severe pruritis .It may manifest with mild diarrhea, epigastric pain
- In Immunocopromised patients large amount of filariform larva are released and may invade :
  - GI tract : causing enteritis with severe diarrhea and malabsorption
  - Lungs: manifest with cough, shortness of breath 9 Loffler's' pneumonia.

- CNS , peritoneum and liver may also be invaded
- Severe systemic symptoms are commonly seen in disseminated infections
- May be complicated by Gram negative sepsis

Drug Treatment

- Ivermectine 200 µg 1-2 days
- Thiabendazole 75 mg/kg bid for 3 days
- Albendazole 400mg/day for 5 days

Skin Manifestations of HIV

- 80-90 % of HIV patients have skin manifestation
- Skin problems could be the first organ system affected
- Various type of skin disease occur

Classification of cutaneous conditions associated with HIV/AIDS

- INFECTIONS: Bacterial infections
- INFESTATIONS
- INFLAMMATORY CONDITIONS
- MALIGNANCY

Staphylococcus auresus

A common pathogenic causes infection

Common manifestations are

- Bullous Impetigo Ecthyma
- Folliculitits
- Furuncle
- Carbuncle , Cellulitis

Treatment:

Topical Antibiotics or Systemic antibiotics depending on severity of the diseases

Syphilis (Treponema pallidum)in HIV infected patients

- Syphilis has atypical presentations in HIV patients
- Primary chancre usually painless can be tender
- Latent period before development of meningovascular syphilis is shorter

- Rapidly progresses to tertiary syphilis
- Relapses without re-exposure
- Pleomorphic skin lesions reported
- VDRL can be negative-due to high titer antibody level

DIAGNOSTIC TESTS

- Screening Tests-VDRL/RPR
- Specific Test-*FTA-ABS*-fluorescent treponemal antibody absorption

Treatment

- Benzathin penicillin 2.4 mega unit IM weekly three doses
- Penicillin IV / 2 to 4 mega unit every 4 hours for 10 to 14 days.(with CNS involvement)
- Azithromycin + Benzathin penicillin + Amoxicillin
- Follow up at intervals of 1, 2, 3, 6, 9 and 12 months.

Viral disease associated with HIV

- Herpes simplex
- Varicella-zoster virus
- Human papiloma virus
- Moluscum contagiosum

Herpes simplex virus

- Is due to reactivation of latent virus
- The usual manifestations are grouped vesicle with erythematous base
- In HIV infected patients however :
    - Atypical presentation
    - Chronic non healing deep ulcer
    - Verrucous erosion
    - Mixed infection are common
    - High frequency of reactivation
    - Widespread local extension
    - Higher incidence of dissemination
    - Viremic spread to visceral organs, which is life threatening

Treatment

- Systemic acyclovir 2oo mg.5 X a day 5-10 days
- Acyclovir 50 mg /kg every 8 hours where absorption is poor
- Acyclovir 400 mg 2 X a day in frequent relapse

- Famcyclovir 125 mg 2 x daily for 5 days
- Valacyclovir 1 gm 2 x daily for 10 days

Varicella-zoster virus (HZ)

- There is increased incidence of HZ in patients with HIV infection
- It is one of the earliest opportunistic infection to occur
- **The clinical presentations are atypical presentation**
    - Hemorrhagic necrotic lesion
    - Chronic verrucous lesion
    - Multiple dermatomal involvement
    - Tendency to be generalized
    - It may occur recurrently

Treatment

Primary varicella-acyclovir IV 10mg /kg every 8 hours for 7 to 10 days

Herpes zoster

- Acyclovir 800 mg 5 X a day for 7 – 10 days
- Famcyclovir 500 mg 5 x /day for 7 days
- Valacyclovir 1 gm 3 x a day for 7 days

Humna papiloma virus

Wart is common infection in HIV

It is refractory to treatment

Complications are neoplastic changes and increased risk of cervical carcinoma

Treatment

- Podophyllin 20 % or 5-Fluorouraacil
- Cryotherapy or Excision of big tumors

Moluscum contagiosum(MC)

Cause by pox virus

It occurs in HIV patients with low CD4 count

Atypical presentations are common

- It is commonly seen in children but can infect immunocopromised adults

- It tends to be Generalized
- Giant Moluscum contagiosum
- Secondary infection

Treatment

- Cryosugery or Curettage or Electrosurgery
- Podophyllin or Cantaridine or 5-fluorouracil

Pruritic papular eruption (PPE)

- It Chronic itchy condition commonly seen in HIV infected patients
- Symmetrical non-follicular papules on trunk and extensors of extremities
- The most common cutaneous manifestation in HIV- prevalence 11-46 %

Diagnosis: Biopsy

Treatment

Topical: Antipruritic lotion, Corticostroid, Oatmeal bath

Systemic: Antihistamin, coricosterroid, Phototherapy, UV-B, UVA + Psoralen

Cytomegalovirus (CMV)

- Cytomegalovirus (CMV)
- Herpes virus
- High incidence
    - 30 - 40% in general population are positive antibody for CMV
    - 90% or more in IV Drug abusers have positive antibody for CMV
    - 20-30 % of patients with AIDS had CMV reactivation prior to the era of HAART
    - Able to establish a latent infection that can reactivate
    - Late-stage AIDS illness (CD+4 < 100)

Clinical manifestations: retinitis, esophagitis, colitis

CMV Retinitis;

- Clinical presentation:Visual disturbances – floaters , flashes of light photophobia and blurring of vision ,painless, gradual loss of vision ,usually bilateral

Diagnosis confirmed by retinal exam

CMV GI Disease

Esophageal ulcers

- Pain and difficulty in swallowing
- Diagnosis by tissue biopsy

Colitis

- Abdominal pain, watery diarrhea, sometimes bloody, rarely perforation
- Fever
- Diagnosis by tissue biopsy

Hepatitis and acalyculus cholecystitis

Treatment for CMV

- Valganciclovir (PO)
- Ganciclovir (IV)
- Ganciclovir Intra-ocular Implant
- Foscarnet (IV)
- Cidofovir (IV)

  18% in IV Ganciclovir

Visceral Leishmaniasis and HIV Co-infection

- Visceral Leishmaniasis is Caused by *L.donovanii*
- VL has become an important OI among persons infected with HIV-1
- Most co-infected patients with clinically evident leishmania have CD4 cell less than 200/µl.
- The infections affect the same cell lines, causing cumulative deficiency of the immune response
- Leishmania parasite suppresses Th1 activity
- Visceral Leishmaniasis Clinical Manifestation
- Patients present with fever, organomegaly, anemia or pancytopenia
- Presentation could be atypical, but VL should be suspected in those with travel history to endemic areas

Diagnosis

- Serology less sensitive in immunocompromised
- Parasite could be detected in peripheral blood in immuno -compromised patients
- Bone marrow aspirate
- Splenic aspirate most sensitive

Treatment

First line – Pentavalent antimonials (Sb)

Alternatives- Pentamidine, Amphotericin B

Relapse and toxicity are common in patients co-infected with HIV

Opportunistic Malignancies

- **Kaposi's Sarcoma**
- **Lymphoma**
- **Cervical cancer**

Kaposi's sarcoma

Etiology/pathogenesis: multi-factorial

- Vascular neoplasm affecting skin and mucosa
- Immunosuppression increases risk of KS 400-500 times higher than general population
- Presence of Human Herpes Virus 8 (HHV8) found in all types of KS
- HIV virus Tat protein potentiates the milieu conducive to KS growth

Transmission

- Studies have shown that HHV-8 which is the etiologic agent for KS is believed to be transmitted sexually. The risk factors are multiple partners, history of STD, and being HIV positive.
- More common in homosexual men
- Multiple heterosexual contacts is a risk factor for HHV-8 in Africa
- Parentral: frequent IVDU
- Oral: via saliva: HHV-8 titers 2-3 times higher in saliva than in semen, anorectal or prostate fluid samples

Epidemiology

- Is the most common Opportunistic malignancy among HIV positive patients
- With use of HAART, KS incidence has declined by 66%

Clinical Manifestations

- Can affect almost any organ system
- Most common sites include

- Skin: flat to nodular lesions; can progress to significant infiltration of skin and necrosis
- Oral cavity: flat to invasive lesions
- GI tract: can have KS anywhere in GI tract, which can cause intestinal blockage and bleeding
- Pulmonary: can spread along bronchi and vessels.

Diagnosis

- Skin and oral lesions can be diagnosed by visual exam even though skin biopsy is most accurate to make diagnosis
- Lung and GI-tract lesions would need endoscopy and biopsy for accuracy
- Resolution of skin lesions with HAART can give a presumptive diagnosis
- Testing for HHV-8 is more research than clinically applicable

Treatment

Primary treatment is antiretroviral drugs (HAART). Lesions significantly regress with HAART

Local therapy for skin lesions

- Alitretinoin gel (35-50% response),Local radiation (20-70% response)
- Intralesional vinblastine/vincristine (70-90% response)
- Cryotherapy (85% response), Photodynamic therapy or Surgical excision

Systemic Treatment*:*

Immunotherapy-*in*terferon-alfa: immunomodulatory antiviral and antiangiogenic. This treatment may have superior efficacy if combined with HAART.

Chemotherapy: Indicated for rapidly progressive oral or visceral disease

- Liposomal doxorubicin/daunorubicin is superior to conventional chemo with less toxicity

Lymphomas

- Lymphomas occur with increased frequency in immunoi deficiency states and there are 120X increased incidence of Lymphoma among HIV patients.
- 6% of all AIDS patients develop lymphoma at sometime in the course of their illness
- As HIV diseases progress the risk of Lymphoma increases.
- The incidence of lymphoma hasn't shown dramatic decrease even after HAART is being widely used by HIV patients worldwide.

- It is a late manifestation which often occurs when the CD4count falls below 200/mm^3

Three main categories seen with HIV

- Grade III or IV Immunoblastic lymphoma (60%)
- Burkitt's lymphoma(20%)- associated to EBV
- Primary CNS lymphoma

Treatment

1. In patients with high CD4 count – Intensive Chemotherapy
   In patients with low Cd4 count – low dose Chemotherapy
2. Palliative measures : to decrease the size of the lesion and associated edema
   - Radiotherapy
   - Glucocorticoides **:**

Cervical cancer

- There is a five-fold risk of developing cervical c.a. in women with AIDS
- Is associated with human papilloma virus infection
- Invasive c.a. of the Cervix is an AIDS defining illness.
- Abnormal PAP smear is seen in 60%of HIV infected women
- Anorectal c.a. may also be seen in homosexual men

Clinical Staging of HIV/AIDS

There are different types of staging systems. The most common are:

- The WHO clinical staging system
- The CDC staging system

WHO Clinical Staging System for HIV/AIDS

- It is a system designed for estimating the degree of immuno-suppression on clinical criteria
- Intended for use in patients known to have HIV (i.e. HIV+ antibody test)
- It is widely used in recourse limited settings to make decisions as to when to start patients on ART
- According to this staging system there are 4 clinical stages

Table I-5-3. Revised classification system for HIV infection (CDC Classification)

CD4 category	*Clinical category*		
	Asymptomatic /Primary HIV	**Symptomatic Not A or C conditions**	**AIDS indicator conditions**
1. > 500/mm^3	**A1**	**B1**	**C1**
2. 200-499 /mm^3	**A2**	**B2**	**C2**
3. < 200 /mm^3	**A3**	**B3**	**C3**

The shaded portion indicates the expanded AIDS surveillance case definition.

Comparison: WHO vs. CDC Classification

- WHO classification does not require CD4 count and hence is more appropriate to use in resource limited settings with high HIV prevalence.
- CDC clinical categories more dependent on expensive laboratories and the staging is not adapted to resource poor settings

Table I-5-4. WHO Clinical Staging System for HIV/AIDS

Stage 1	***Asymptomatic***
Stage 2	***Minor Symptoms***
Stage 3	***Moderate Symptoms***
Stage 4	***AIDS defining illnesses***

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)(PGL-is defined as the presence of lymph node > 1cm, in two extra inguinal sites and persisting for more than three months)

Clinical Stage 2s

- Unexplained moderate weight loss (< 10 % of body weight)
- Recurrent upper respiratory tract infections (sinusitis , tonsillitis , otitis media , and pharyngitis)
- Minor mucocutaneous manifestations (seborrheic dermatitis, fungal nail infections, recurrent oral ulcerations, angular chelitis)
- Herpes zoster within the past 5 years (single dermatome)

Clinical Stage 3

- Unexplained sever weight loss (>10% of body weight)
- Unexplained chronic diarrhea longer than 1 month
- Unexplained prolonged fever > 1 month
- Persistent Oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infection (pneumonia, pyomyositis, empyema, meningitis, bateremia)
- Acute necrotizing ulcerative stomatitis, ginigivitis, or periodentitis
- Unexplained anemia (< 8 gm/dl), neutropenia 500/$mm^{3,}$ and or chronic thrombocythopenia (< 50, 000/mm)

Clinical Stage 4

- HIV wasting syndrome
- Pneumocystis carinii pneumonia
- CNS toxoplasmosis
- Cryptosporidiosis or Isosporosis related watery diarrhea > 1 month ,
- Extrapulmonary cryptococcosis
- Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or lymph nodes (e.g. retinitis)
- Chronic Herpes simplex (HSV) infection – orolabial, genital anorectal lasting for more than 1 month

- Any disseminated endemic mycosis (e.g. histoplasmosis, coccidiodomycosis)
- Esohagial Candidiasis (involving esophagus, trachea, bronchi or lungs)
- Recurrent Bacterial pneumonia
- Recurrent septicemia
- Disseminated atypical mycobacterium
- Extrapulmonary tuberculosis
- Lymphoma (cerebral or B-cell Non Hodgkin's lymphoma)
- Invasive cervical carcinoma
- Kaposi's sarcoma
- HIV encephalopathy
- Symptomatic HIV associated neuropathy.

Antiretroviral Drugs (ARTs)

ARTs are the corner stone of medical management of HIV infection.

Classes of Antiretroviral Drugs

1) Nucleoside reverse transcriptase inhibitors (NRTIs)

Lamivudine (3TC)	Stavudine (d4t)
Zidovudine (AZT	*Abacavir (ABC)*
Didanosine (DDI)	*Zalcitabin (DDC)*
Emtricitabine (FTC)	*Tenofovir (TDF),*

Mechanism of Action: Structurally these drugs resemble naturally occurring nucleosides and break the formation of viral DNA by breaking the chain (chain breakers)

Zidovudine (AZT)

- **Dosage**:*300mg PO BID*
- ***Side effects:*** Anemia, Myalgias, bone Marrow Suppression

Lamivudine (3TC):

- **Dosing**: 150mg BID or 300mg QD
- **Side effects** :Headache , occasional nausea

Stavudine (d4T)

- **Dosing**: 40 mg BID for weight > 60 kg , *30 mg BID for weight < 60 kg*
- **Side effects** :Peripheral Neuropathy (5-15%) ,Lactic acidosis, Pancreatitis

Abacavir (ABC)

- **Dosing**: 1 x 300mg tablet BID
- **Toxicity:** Allergic reaction (Hypersensitivity reaction) which occurs within first 6 weeks of initiation of therapy. Never re challenge the patient again with ABC

***Tenofevir (TDF**): is a*ctually, a nucleoTIDE

Dosing: 1 x 300mg tablet QD

Toxicity: Headache, Nausea, Diarrhea, Lactic acidosis

Didanosine (ddI)

Dosing

1 x 400mg enteric coated capsule QD (if <60kg: 250mg QD)

Or

2 x 100mg buffered tab BID or 4 x 100mg QD (if <60kg: 125 mg BID or 250mg QD)

***NOTE**: If use buffered tablets, 2 or more tablets must be used at each dose to provide adequate buffer*.

Or

250mg of reconstituted buffered powder BID (if <60kg: 167mg BID)

Didanosine (ddI) (2)

Food Interactions: take on empty stomach

Toxicity: Peripheral Neuropathy, Nausea, abdominal pain, Pancreatitis, Lactic acidosis

2) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- **Nevirapine (NVP, Nevipan®)**
- **Efavirenz (EFV, Stocrin®)**
- *Delavirdine (DLV, Rescriptor®), rarely used*

***Mechanism of Action:** inhibit the active site of Reverse transcriptase enzyme*

Nevirapine (NVP, Nevipan®)

Dosing: 200 mg QD x 2 weeks, then 200 mg BID

Toxicity:

- **Skin rash (17%)** may be
    - ***Milder form (dry rash)*** : erythematous, maculopapular rash
        - Treatment: continue medication with close observation antihistamins may be administered
    - ***Severe form (wet rash)***: with mucous membrane involvement, Steven's Johnson Syndrome and Toxic epidermal necrolysis (TEN)
        - Rx:- Discontinue medication, never re-challenge

- ***Hepatitis :***

Efavirenz (EFV, Stocrin®)

***Dosing*:** 3 x 200mg capsules or 600mg P.O. /d

Food Interactions: Take with low-fat meal because high-fat meals increase absorption by 50% → increases side effects

Toxicity

- **CNS Changes** (52%) - Insomnia, nightmares, poor concentration, mood change, dizziness, disequilibrium, depression, psychosis
- ***Skin Rash*** (15-27%)- usually does not require discontinuation
- Nausea

CONTRAINDICATED DURING PREGNANCY

3) Protease Inhibitors

Lopinavir + Ritonavir (Kaletra®)	Nelfinavir (Viracept®)
Saquinavir-SGC (Fortovase®)	Saquinavir-HGC (Invirase®)
Indinavir (Crixivan®)	Amprenavir (Agenerase®)
Fosamprenavir (Lexiva®)	Atazanavir (Reyataz®)
Ritonavir (Norvir®)	

Mechanism of Action: Inhibit viral assembly by blocking the

- PIs are mainly used as second line drugs in recourse limited settings as these drugs are expensive and most formulations need refrigeration.

Common side effects of PIs

- Glucose intolerance (in some patients may cause Diabetes mellitus)
- Lipid abnormalities :hypertriglyceridemia , low HDL and high LDL
- Lipodystrophy-– Morphologic Changes ,fat accumulation in the lower part of the body and atrophy of facial fat

***Goals of ART: (HAART* = Highly Active Antiretroviral Therapy)**

1) Improve the length and quality of the patient's life
2) Increase total lymphocyte count (TLC) and CD4 cell count, allowing preservation or improvement of immune function
3) HIV RNA < 400 copies/ml or "undetectable" within 4-6 months of ART initiation
4) Reduce HIV-related morbidity and mortality

❖ Is not a cure for HIV. If treatment is stopped, the virus will continue to replicate

❖ It cannot eliminate HIV completely from the body.

What does HAART require to be effective?

- Strict adherence to this regimen
- Proper monitoring of side effects and disease progression
- Recognition and treatment of co-morbidities
- Recognition of drug interactions

The Baseline Assessment before initiation of HAART

- ❖ Baseline medical history
- ❖ Physical examination
- ❖ Clinical staging
- ❖ Laboratory testing
- ❖ Development of the patient care plan

WHO Criteria to Initiate ART in Adults and adolescents

WHO clinical stage	***CD4 testing not available***	***CD4 testing available***
1	Don't treat	Start ART only if CD4 count is < 200/mm^3
2	ART may be started if TLC is < 1200/mm^3	
3	If symptomatic initiate ART irrespective of TLC	Start ART if CD4 is< 350/mm^3 and initiate before CD4 drops <200/mm^3
4	Start ART irrespective of TLC	Start ART irrespective of CD4 count

Note: ART should be initiated in WHO clinical stage 3 patients with CD4 <350/mm^3 if patients have:

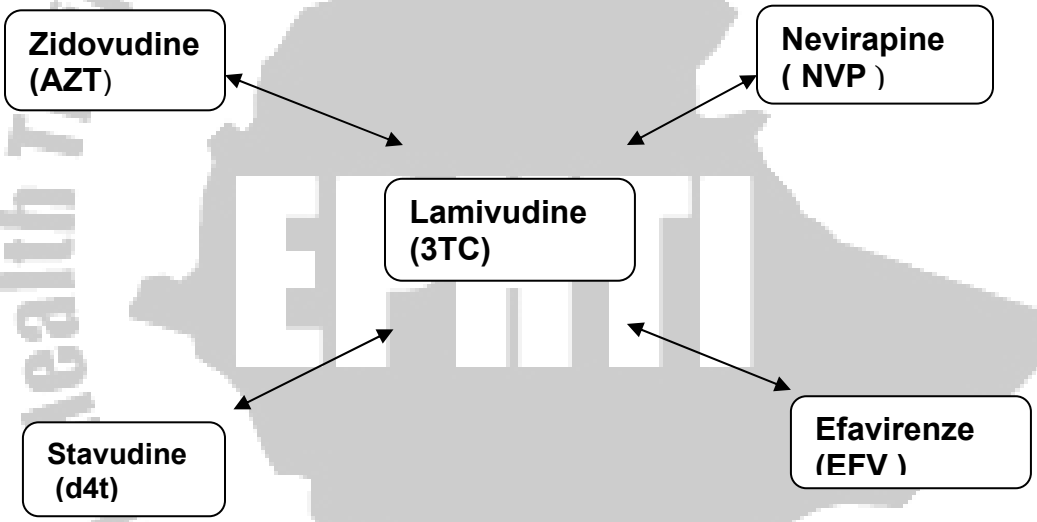
- o Pulmonary TB
- o Sever bacterial infections

- Oral candidiasis

Do not start ARVs if:

- The patient is not motivated
- Without intensive counseling
- If treatment cannot be continued
- If asymptomatic and no information about CD4+ count
- If the patient has active OI (first treat the OI which may be an immediate danger to the life of the patient before initiating ART)
- If the patient has serious psychiatric illness and there is no care giver

First-Line ARV Regimen for Ethiopia



Four combinations can be made from these first line drugs

- AZT/3TC/NVP or
- AZT/3TC/NVP or
- D4T/3TC/EFV or
- D4T/3TC/EFV

Second Line drugs for Ethiopia

ABC or TDF or ZDV (if not taken)/+ Didianosin (ddI) + Kaletra® LPV/r or SQV/r or NFV

The indications for changing from First line to Second line regime is when there is evidence of treatment failure

- Clinical failure
- Immunological failure
- Virological failure

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6. Sexually transmitted Infections

Learning objectives: At the end of this lesson students are expected to

1. *Define Sexually transmitted diseases (STDs or STIs)*
2. *Understand the common etiologic agent for STIs*
3. *Understand the epidemiology of different STIs*
4. *Describe the pathophysiology of common STIS*
5. *Identify the clinical manifestations of different STIs*
6. *List the complications and Organ systems affected by STIs*
7. *Describe the most commonly investigations for the diagnosis of STIs*
8. *Make an appropriate diagnosis of Different STIs*
9. *Understand the syndromic approach for the management of different STIs*

Definition:

Sexually transmitted diseases (STD'S) are a diverse group of infections, caused by different types of microbial agents, that are frequently transmitted by sexual contact, and for which sexual transmission is epidemiologically important, are considered sexually transmitted diseases. "Sexual" includes the full range of heterosexual or homosexual behavior, including genital, oral-genital, oral-anal, and genital-anal contact.

- At present there are more than 20 known causes of STD. No single STD can be regarded as an isolated problem because multiple infections are common and because the presence of one STD denotes high-risk sexual behavior that is often associated with other, more serious infection.
- Most STDs are rarely if ever transmitted by fomites, food, flies, or casual contact.
- At least one sexual partner is always infected; the apparent exceptions usually can be attributed to prolonged sub-clinical infection in one or both partners. Therefore, risk assessment (including elicitation of a sexual history) and management of sexual partners are of paramount importance.

Epidemiology of STIs

- STIs are major public health problems in all countries, but are especially in developing countries where access to adequate diagnostic and treatment facilities is very limited or nonexistent. There is limited information on the incidence and prevalence of STIs is

Ethiopia. FMOH compiled 58,632 and 27,947cases from all regions in 2002 and 2003 respectively.

- A large proportion of STIs are symptomatic and most symptomatic patients seek treatment from traditional healers , pharmacists , drug vendor shops and market places
- STDs can be classified and managed in two different ways (approaches)

1. ***Etiologic approach***
   - ***Advantages:*** Accurate diagnosis, accurate treatment, proper use of antibiotics (decreases over treatment and antibiotic resistance). It is the better way to diagnose and treat asymptomatic infections
   - ***Disadvantages***: Needs lab support and expertise , expensive (cost may be incurred due to lab tests) and it is time consuming
2. ***Syndromic approach***
   - ***Advantages:*** Treatment can be given immediately, mixed infection may exist and may be adrsessed, there is no need for laboratory diagnosis and the treatment can be given by middle level health professionals. Hence this approach may be a good alternative for in resource limited settings.

   Disadvantages: over treatment with antibiotics, there is risk of creating antibiotic resistance and decreased compliance. There is also increased cost of drugs. Moreover asymptomatic infection missed.

N.B – In general, an overall approach to the management of a patient with sexually transmitted disease begins with

Risk assessment of:

- Sexual orientation and practice
- Number of recent and current sexual partners
- History of STD in the patient
- Recent history of STD of the partner
- Sociodemographic and other markers of high risk

Clinical assessment: elicitation of information on specific current symptoms and signs of STDs.

Laboratory tests: If available, confirmatory diagnostic or screening tests may then be ordered.

Comprehensive Case Management*:* is vital approach for controlling STIs. So health care providers should undertake the following measures besides treating individual patients

1. Partner notification and management
2. Condom promotion and supply
3. Health education and risk reduction counseling
4. Linkage with HIV counseling and testing
5. Follow-up visits for patients with STI

STI Syndromes

- *Urethral discharge Syndrome*
- *Vaginal discharge*
- *Genital ulcer*
- *Inguinal bubo*
- *Scrotal swelling*
- *Lower abdominal pain*
- *Neonatal conjunctivitis*

1. Urethral discharge:

Urethral discharge is the most common presenting compliant of men with STD. In urethral discharge, exudate is present in the anterior urethra and the discharge is often accompanied by dysuria or urethral discomfort. It may lead to epididymitis and complications such as infertility and urethral stricture.

Etiology

For practical purposes, STD-related urethritis is divided into

- ***Gonococcal urethritis: caused by Nisseria gonorrhea***
  - Has a short incubation period (2-3days
  - Vast majority of cases present with abundant and purulent discharge
  - Tend to produce more severe urinary tract infection symptoms like dysuria, urgency and frequency.
- ***Nongonococcal urethritis (NGU):*** usually caused by Chlamydia trachomatis or U.urealyticum.
  - Has scanty to moderate, white, mucoid or serous discharge.
  - Mild urinary tract infection symptoms
  - Has long incubation period (1-3 weeks).

The quantity and appearance of the discharge can be used to distinguish accurately gonococcal and nongonococcal urethritis in about 75-80% of patients who have not urinated recently. It can't, of course, be used to diagnose dual infection with N.gonorrhea and C.trachomatis. Milking of the urethra may be necessary to get a good amount of discharge sample.

Laboratory

- Microscopy of urethral discharge stained with methylene blue or safranin or Gram's stain shows pus cells with characteristic intracellular coffee bean shaped diplococci → N.gonorrhea.
- Pus cells without intracellular diplococci = NGU.

Treatment:

When the accurate etiologic diagnosis is made

- **Gonococcal Urethritis**:
  Ceftriaxone 250mg IM stat
  OR
  Ciprofloacin 500mg PO stat
  OR
  Spectinomycin 2mg IM stat.
- ***NGU***: Doxycycline 100mg PO BID for 7 days or Tetracycline 500mg PO QID for 7 days OR Erythromycin 500mg PO QID for 7 days if the patent has contraindication for TTC..

When there is no Etiologic diagnosis: Treatment should cover both gonococccal and chlamydial infections (combine the above treatments)

2. Vaginal Discharge:

Etiology

1. *N.gonorrhea*
2. *Chlamydia trachomatis*
3. *Trichomonas vaginalis,*
4. *Gardnerella vaginalis*
5. *Candida albicans*
6. *Vaginal anaerobes ("bacteria vaginosis")*
   - *The first three are sexually acquired and the last three are endogenous infections.*
   - *The first two cause cervicitis while the last four cause vaginitis.*

- *Bacterial vaginosis (Gardnerella vaginalis) is the leading cause of vaginal discharge in Ethiopia followed by Candidiasis, Trichomoniasis, and Gonococcal and Chlamydial cervicitis.*
- As urethritis in males, co-infection with C.trachomatis is common in women with gonorrhea (~ 50%).

Clinical feature:

Many women have a small amount of vaginal discharge (physiologic leukorrhea), which is clear and odourless. It becomes abnormal if the woman notes a change in the amount , colour or odour of the discharge . In general, most women with this syndrome will complain of:

- Excessive secretions and soiling of undergarments
- Changes in colour and/or odour of discharge
- Associated itching, dysuria, dysparunia
- Redness of vulva
- Sometimes may be accompanied by lower abdominal pain

The initial assessment of a patient who has vaginal discharge includes risk assessment and clinical evaluation with speculum examination to determine the site of infection.

Vaginitis: bacterial vaginosis, vaginal candidiasis and /or trichomoniasis are the usual causes of vaginitis.

- Bacterial vaginosis and trichomoniasis are more frequent among sexually active women while vaginal candidiasis occurs when there is impairment of local or systemic defense mechanism.
- The discharge in bacterial vaginosis is homogenous with a typical fishy odour due to the presence of volatile amines and this may e apparent during examination or when the discharge is mixed with 10 % KOH.
- Trichomonads present with profuse, runny, mal-odorous discharge. Yeasts (Candida) often present with white, curd-like discharge and pruritus.

Speculum examination: in isolated vaginitis the cervix looks healthy and discharge is not coming from the cervical opening.

Cervicitis: The presence of purulent exudates from the cervical os indicates infection with *N.gonorrhea* and *C.trachomatis.*

Risk factors for STI related cervicitis in Ethiopia (one or more of the following)

- Multiple sexual partners in the last 3 months

- New sexual partners in the last 3 months
- Age less than 25 years
- Having ever traded sex

Cervicitis is frequently asymptomatic. It may be detected on routine pelvic examination or during evaluation of a patient with vaginal discharge

Complications of Cervicitis and Vaginitis

- PID
- Premature rapture of membrane
- Preterm labour
- Infertility
- Chronic pelvic pain

Laboratory:

It is used mainly for the diagnosis of trichomoniasis, bacterial vaginosis and candidiasis

T.vaginalis*:* characteristic jerky motility of the parasite with many leukocytes.

B.vaginosis*:*

- The typical fishy odour will be enhanced by the addition of 1- 2 drops of KOH to the specimen of vaginal discharge ("sniff test")
- Number of epithelial cells per microscopic field exceeds the number of leukocytes.
- "Clue cells" =cornified squamous epithelial cells covered by coccobacilli.

Candidiasis: Look for yeast (10% KOH may improve diagnostic sensitivity).

N.B. In general, Gram stains are not helpful in diagnosing gonorrhea in females (low sensitivity).

Treatment

When accurate Diagnosis is made

T.vaginalis : Metronidazole 2gm PO stat

B. Vaginosis

- Only symptomatic women need treatment.
- Metronidazole 500mg PO BID for 7 days or Metronidazole 2 gm as single dose and repeat after 48hr.

Vulvovaginal candidiasis

Topical antifungal agents: Nystatin 100,000-1,000,000 IU, intravaginally daily for 14 days.

Miconazole or clotrimazole 200mg intravaginally daily for 3 days

Mucopurulent discharge from the cervix : treat for gonorrhea and chlamydial infection.

When Specific diagnosis could not be made manage as vaginal discharge syndrome

Recommended treatment for Vaginal Discharge	
Risk Assessment Positive	***Risk Assessment Negative***
Ciprofloxacin 500 mg PO stat **Or** Spectinomycin 2gm IM stat **Plus** Doxycycline 100 mg PO BID for 7 days **Plus** Metronidazole 500mg Po ID for 7 days	Metronidazole 500mg Po ID for 7 days ***Plus*** Clotrimazole vaginal tabs 200mg at bed time for 3 days

3. Genital Ulcer:

A genital ulcer is a loss of continuity of the skin of the genitalia.

Genital ulcers may be painful or painless and are frequently accompanied by inguinal lymphadenopatly.

Common Etiology agents:

- *Treponema pallidum (syphilis)*
- *Haemophilus ducreyi (chancroid)*
- *Calymmatobacterium granulomatis (granuloma inguinale)*
- *C.trachomatis serovar L_1-L_3 (Lymphogranuloma venereum or LGV)*
- *Herpes virus 1 or 2 (Herpes simplex virus or HSV)*

Syphilis

- Genital ulcer occurs in the primary stage of the diseases
- It starts as a small popular lesion that rapidly ulcerates to produce a non tender indurated lesion with a clean base and raised margins known as chancre
- Chancres may appear at any point of contact :genitals, anus, mouth, lips
- Heal without treatment in 1 to 6 weeks
- Swollen lymph nodes may appear

Complications

- Secondary syphilis
- Aortitis with valvulitis
- Neurosyphilis

Genital Herpes:

- HSV virus has two types
  - HSV-2 causes dominantly genital disease
  - HSV-1 causes dominantly oral disease
- Worldwide the most common cause of genital ulcer
- Latency and frequent recurrence characterizes genital herpes , producing a lifelong infection /persistent
- Herpetic ulcers
  - Are usually painful and multiple
  - Starts as clear vesicle and becomes pustule, which later erodes to an ulcer and then crusts
  - Heals spontaneously after 2-3 weeks
  - Recurrence possible but milder (number of vesicles are fewer)
- It tends to be aggressive in HIV patients with extensive tissue involvement and chronic ulceration. It may also be dissemination to CNS, skin etc

Complications:

- Recurrence
- Aseptic meningitis and enchephalitis

Chancroid

- Caused by *Haemophilus ducreyi*
- Is one of the commonest causes of genital ulcer in most developing countries, however it was not found to be a common cause of genital ulcer in Ethiopia.
- Incubation period: 3 -15 days
- Ulcer on the penile shaft or prepuce
- It is painful progressing from a small papule to pustule and then ulcer with soft margins described as soft chancre , yellow gray exudative covering and erythema
- Inguinal adenopathy that becomes necrotic and fluctuant (bubo) follows the ulcer within 1-2 weeks

Complication: penile autoamputaion

Lymphogranuloma Venereum (LGV)

- Caused by *L1, L2 and L3 serovars* of *Chlamydia trachomatis*
- There is little evidence on the prevalence of LGV in Ethiopia
- Major pathology occurs in the lymphatic system
- ***Primary stage*** is marked by a painless vesiculo-papular ulceration at the site of inoculation
  - Located in the penis in men
  - On the labia and posterior vagina in women.
- Primary lesion usually not noticed.
- ***The secondary stage*** is described as the inguinal syndrome
  - A painful inguinal lymphadenitis with constitutional symptoms
  - In men infection usually spreads through the lymphatics causing inguinal and femoral lymphadenitis.
  - In women upper vaginal and cervical infection results in enlargement of the obturator and iliac nodes. (sometimes pelvic nodes)
- Inguinal adenopathy is usually unilateral (2/3 of cases)
- Nodes initially discreet later becomes fluctuant and suppurative developing multiple draining fistulas
- Bubo may be grooved by the inguinal ligament ("groove sign" of LGV)
- External genitalia may be oedematous and swollen
- May lead to anatomical distortion and irregularity, particularly of the penis
- Spontaneous healing after several months possible

Late complications include

- Genital elephantiasis
- Adhesion
- Stricture and fistula of the penis, urethra and the rectum

Granuloma Inguinale (Donovanosis)

- Chronic: progressively destructive bacterial infection of the genital region without systemic symptoms
- Etiology: *Calymmatobacterium granulomatis* a gram-negative intra-cellular bacteria
- Transmission –sexual and non-sexual contact

- Distribution –mainly in Australia, Caribbean, India, and southern Africa. Little information about its prevalence in Ethiopia

Clinical Manifestation

- Incubation period – usually1 to 4 weeks may be as long as a year
- The patient usually presents with a non suppurative genital lesion which develops from a small firm papule to painless ulcer with a beefy-red appearance and non-purulent base
- Lesion bleeds easily, expand gradually
- Extra inguinal in 6% of cases
- 50% women have lesion on cervix

Complications

- Genital pseudo-elephantiasis of labia
- Adhesion
- Urethral , vaginal or rectal stenosis

Management of Genital Ulcer

1. When specific Etiologic diagnosis is made

Syphilis:

- Benzanthine penicillin 2.4million IU IM stat OR
- Procaine penicillin 1.2million IU daily IM for 10 days.
- In penicillin allergic patients, doxycycline 100mg PO BID for 15 days or Tetracycline 500mg PO QID for 15 days.

Genital Herpes:

- Acyclovir 200 mg 5X per day for 10 days or Acyclovir 400 mg Po TID for 10 days

Treatment of chancroid:

- Ceftriaxone 250mg 1M stat or
- Erythromycin 500mg PO TID for 7 days

Treatmen of LGV:

- Doxycycline 100mg PO BID for 14 days or
- Tetracycline 500mg PO QID for 14 days

Treatment of Granuloma inguinale

- Cotrimoxazole 02 tab PO BID for 14 days

N.B – Tetracycline is contraindicated during pregnancy

2. When specific Etiologic diagnosis is not made – Syndromic approach

Recommended treatment for non-vesicular genital ulcer

Benzanthine penicillin 2.4million IU IM stat

Or (in penicillin allergic patients)

Doxycycline 100mg PO BID for 14 days

Plus

Ciprofloxacin 500 mg PO for 3 days or

Erythromycin 500mg PO QID for 7 days

Recommended treatment for Vesicular, multiple or recurrent genital ulcer

Acyclovir 200 mg 5X per day for 10 days or

Acyclovir 400 mg Po TID for 10 days

Recommended treatment for

Recurrent Infection: Acyclovir 400 mg Po TID for 5 days

Suppressive therapy: Acyclovir 400 mg PO BID continuously

4. Lower abdominal pain:

Lower abdominal pain in women is associated with pelvic inflammatory disease (PID).PID denotes pelvic infections in women (e.g. salphingitis, endometritis, parametritis, oopheritis) caused by microorganisms which generally ascend from the lower genital tract to invade the endometrium, fallopian tubes, ovaries, other adjacent tissues and peritoneum

Etiology:

- Commonly N.gonorrhea and C.trachomatis which are sexually transmitted
- PID if often polymicrobial and may be associated with Mycoplasma , Bacteriods , Streptococcus , E.Coli , H .Influenza which may or may not be sexually transmitted

Risk factors:

- The occurrence of vaginal discharge may be an antecedent event
- STD
- postpartum and postabortal ascending infections
- Intra uterine device (IUD)

Clinical feature:

- Mild to severe bilateral lower abdominal pain is the most common complaint, which may first be noticed during or shortly after the menses and which is sometimes associated with fever.
- The presence of vaginal discharge supports the diagnosis of PID and pain during intercourse or urination may also be present

Physical examination

- Lower abdominal and adenexal tenderness together with cervical excitation tenderness may be indicative of PID.
- A tender pelvic mass together with fever, nausea or vomiting can also be detected.
- Vaginal discharge, genital ulcer, presence of IUD, open cervix (abortion tissue seen or felt) support the diagnosis of PID.

Diagnosis:

- Is often difficult. Over diagnosis and treatment may be justified in order to prevent complications.
- Rule out other cause of lower abdominal pain in women such as appendicitis , ectopic pregnancy and Cholecystitis

Laboratory: Direct wet mount microscopy of a vaginal specimen is necessary. The presence of pus cells in numbers exceeding those of epithelial cells suggests infection of the lower genital tract.

Complications

- Peritonitis and intra-abdominal abscess
- Adhesion and Intestinal obstruction
- Ectopic Pregnancy
- Infertility

Treatment

Most patients with mild to moderate PID can be treated as an out patient

Some patients need hospital admission: Indications for admission are

- Uncertain diagnosis
- Pelvic abscess suspected
- Pregnant patients
- Co infection with HIV

- As the infection is poly-microbial in nature instead of single, combination of antibiotics should be prescribed. The spectrum of activity of the antimicrobial agents should cover the following organisms: *N.gonorrhea, C. trachamatis, aerobic and anaerobic bacteria.*
- *A*ntibiotics should be initiated empirically even before the microbiological report is available.

Recommended treatment for PID	
Out patient	***In patient***
Ciprofloxacin 500 mg PO stat **Or** Spectinomycin 2gm IM stat **Plus** Doxycycline 100 mg PO BID for 14 days **Plus** Metronidazole 500mg Po ID for 14 days ***Admit the patient if there is no improvement within 72 hours***	Metronidazole 500mg Po ID for 7 days ***Plus*** Clotrimazole vaginal tabs 200mg at bed time for 3 days

Non Specific: Adequate bed rest, analgesic,

If there are any obstetric or surgical complications, refer the patient as early as possible.

5. Inguinal bubo:

- Inguinal bubo is an enlargement of the lymph glands in the groin area.
- Etiology: The common sexually transmitted pathogen associated with Inguinal bubo include
    - *C.trachomatis serovar L_1-L_3 (Lymphogranuloma venereum or LGV)*
    - *Haemophilus ducreyi (chancroid)*
    - *Calymmatobacterium granulomatis (granuloma inguinale)*
    - *Treponema pallidum (syphilis) may sometimes cause inguinal bubo*

- Except in case of LGV, a bubo is rarely a sole manifestation of STD and is usually found together with the etiologically related genital ulcer. Non-sexually transmitted local or systemic infections can also cause inguinal lymphadenopathy.

Clinical feature:

- Usually patients complain of unilateral or bilateral painful swelling in the groin, but buboes can be painless.
- It is important to ask for any history of associated genital ulcer.

Treatment:

Recommended treatment for Inguinal Bubo
Ciprofloxacin 500 mg PO BID for 3 days PLUS Doxycycline 100 mg PO BID for 14 days OR Erythromycin 500 mg PO BQID for 14 days

- Fluctuant buboes require aspiration through adjacent healthy skin (don't incise for drainage).
- If genital ulcers are present, treat with the etiologically related cause of the ulcer.

6. Scrotal Swelling Syndrome

The cause of scrotal swelling depend on the age of the patient

For those younger than 35 years

- *N.gonorrhoeae*
- *C.tracomatis*

For those older than 35 years

- *Gram negative organisms*
- *Tuberculosis*
- *Other cause include : Brucellosis , Mumps , Onchocerciasis , Wuchereria buncrofti*

It is important to exclude other causes of scrotal swelling which may require urgent surgical evaluation and management

- *Testicular Torsion*
- *Trauma*
- *Incarcerated inguinal hernia*

Complications of Scrotal Swelling: caused by STI include

- *Epididymitis*
- *Infertility*
- *Impotence*
- *Prostatitis*

Treatment of Scrotal swelling suspected of STI origin is similar to Urethral discharge.

Recommended treatment for Scrotal swelling
Ciprofloxacin 500 mg PO stat OR Spectinomycin 2gm IM stat PLUS Doxycycline 100 mg PO BID for 7 days OR Tetracycline 500 mg PO QID for 7 days

Supportive Treatment*:* Analgesia and scrotal support may be indicated if the patient has severe pain

References:

1. National guideline for Syndromic aproch of Sexualy transmited infections, Federal MOH, 2005.
2. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Sexualy transmited diseases, overview, pages 762-774

7. Other Important Infectious Diseases

7.1. Tetanus

Learning Objective: At the end of this unit the student will be able to

1. *Define tetanus*
2. *Classify tetanus*
3. *Mention the etiology of tetanus*
4. *Describe the mode of transmission of tetanus*
5. *Explain the epidemiology of tetanus*
6. *Describe the pathophysiology of tetanus*
7. *Identify the clinical manifestations of tetanus*
8. *Describe the most commonly used method for the diagnosis of tetanus*
9. *Make a diagnosis of tetanus*
10. *Refer cases of tetanus to hospitals for better care and close follow up*
11. *Design appropriate methods of prevention for tetanus*

Definitions

Tetanus is a neurologic disease characterized by increased muscle tone and spasms caused by toxin released from the bacteria *Clostridium tetani.*

Etiologic Agent

- *Clostridium tetani* is an anaerobic, motile Gram-positive rod that forms an oval, colorless, terminal spore, which looks like a tennis racket or a drumstick. It is found worldwide in soil.
- Spores may survive for years in soil. They are also resistant to different disinfectant and even to boiling for less than 20 minutes.

Epidemiology

- Tetanus occurs sporadically and almost always affects non-immunized persons. Partially immunized persons or fully immunized individuals who fail to maintain adequate immunity are also affected.
- Tetanus is more prevalent in developing countries like India, Bangladesh, Pakistan, eastern Mediterranean, South America and Africa including Ethiopia.

- Tetanus is more common in rural areas where there is frequent contact with soil. It also occurs more frequently in warmer climates, during summer months and in males. Neonates and young children are affected more in developing countries where immunization programs are not comprehensive. Development of severe illness is seen more in the elderly. Most cases of tetanus follow injuries especially during farming, gardening or other outdoor activities. Tetanus may also be associated with surgery, otitis media, abortion or delivery.

Pathogenesis

- Although C. tetani frequently contaminates wounds, germination and toxin production, however, takes place in wounds with necrotic tissue, foreign bodies or infection that is active. Often the wound is trivial or could seem to be healed from outside.
- *Tetanospasmin, a* toxin produced by the bacteria in the wound binds to peripheral motor neuron terminals, enters the axon and is taken to spinal cord and brainstem by retrograde transport. The toxin then inhibits release of inhibitory neurotransmitter and γ-aminobutyric acid (GABA) with diminished inhibition, there will be increased excitation spasm and rigidity. Tetanospasmin may also block neurotransmitter release at the neuromuscular junction and produce weakness or paralysis. Generalized tetanus occurs when toxin enters into blood stream and lymphatic to affect distant nerve endings.

Clinical Manifestations

- ***The incubation period*** (time between the injury and first symptom) of tetanus is about 7 – 10 days but it may range from 1 day to 2 months.
- ***The period of onset*** (time between the first symptom and spasm) ranges 1 – 7 days.

The shorter the incubation period and period of onset, the more severe the disease becomes. There are different forms of tetanus: neonatal, generalized and localized tetanus. The most common form is generalized tetanus.

Generalized Tetanus

- The median time of onset after injury is seven days; but could occur as early as with in three days. Usually the fist symptom is increased tone in the masseter muscle (trismus, or lockjaw) and patient is unable to open his mouth.

- Immediately after this the patient develops dysphagia, stiffness in the neck and back.
- Then the patient develops contraction of facial muscles to produce rhesus sardonicus (sneer or grimace).
- There may be arched back (opisthotonos), generalized muscle spasm triggered by stimulus such as light or noise.
- Deep tendon reflexes may be exaggerated.
- There may be dysphagia or paralytic ileus.

Localized tetanus: is a rare form of tetanus.

- It presents with rigidity and spasm around the portal of entry.
- While most localized tetanus have good prognosis, cephalic tetanus has high mortality. It comes after head injury, injury to the face or ear infection.

Patients may come with wide ranges of wound severity, although most have trivial or healed wound. In fact 15% – 20 % of patients may not give history of injury.

Neonatal tetanus:

- Occurs in neonates of non-immunized mother and those delivered in unhygienic condition.
- It is a very severe form of tetanus with more than 90% mortality.
- Neonates should be referred urgently to a near-by hospital if there is suspicion of clinical tetanus.

Tetanus may be graded according to severity. Grading is helpful in prognosis and management.

- **Grade I (mild)** : moderate trismus, generalized spasticity
- **Grade II (moderate)** : Moderate trismus, mild to moderate but short lasting spasms, tachypnea – RR 30-35/min and mild dysphagia
- **Grade III (severe)** : Severe trismus, generalized spasticity, prolonged spasms, respiratory embarrassment RR >40/min, apnoeic spells, tachycardia >120/min and severe dysphagia
- **Grade IV (very severe)** : Features of grade III plus severe autonomic disturbance of CVS. It includes episodes of hypertension and tachycardia alternating with relative hypotension and bradycardia or severe persistent hypertension (DBP >110 mmHg) or severe persistent hypotension (SBP <90mmHg).

Poor prognostic factors in Tetanus:

- Patients with higher grades
- Short incubation period and period of onset
- Cephalic tetanus and
- Patients with comorbidities have poor prognosis.

Diagnosis

The diagnosis of tetanus rests entirely on clinical grounds. But wounds should be cultured for C.tetani or superinfection. CSF analysis is normal.

Treatment

The goals of treatment are

- To eliminate source of toxin
- Neutralize unbound toxin and
- Prevent muscle spasm.

General measures:

- Patients should be admitted to a quiet room in an ICU, where frequent monitoring is possible.
- If there are wounds, they should be explored and cleaned.
- ***Respiratory care:*** Intubation and tracheostomy may be required and should be done as early as possible if indicated. These procedures are required for hypoventilation caused by laryngospasm or over sedation or to avoid aspiration.
- ***Autonomic dysfunction***: No definitive treatment has so far been outlined. But hypotension requires fluid expansion and vasopressor agents.
- **Other measures:** hydration should be maintained. Naso-gastric tube can be inserted for nutrition. Physiotherapy should be instituted as soon as possible to avoid contracture. Input and output should be monitored. Bedsores and other infections should be prevented. Recovering patients should start active immunization against tetanus.

Specific Treatment;

***Antibiotic treatment*:** This helps to eradicate the vegetative bacteria, not the toxin.

- Crystalline penicillin 3 million units IV 6X a day for 10 days is used but metronidazole 500mg every 6 hrs or 1g every 12 hours can also be used. Erythromycin and clindamycin are alternatives in patients allergic to penicillins.

Antitoxin: - This neutralizes only circulating toxins which are not bound.

- Human tetanus immune globulin (TIG) is the choice and if available should be given early.
- But tetanus antitoxin (TAT), which is available in our setup, can be given in doses of 10,000 IU intravenous and 10,000 IU intra-muscular.

Control of muscle spasms:

- Diazepam and Chlorpromazine are given 6 hourly, alternatively.
- If spasms are not controlled by the above medication, neuromuscular blockers and mechanical ventilation can be used.

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Tetanus, pages 840-841

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7.2. Rabies

Learning Objective: At the end of this unit the student will be able to

1. *Define rabies*
2. *Mention the etiology of rabies*
3. *Describe the mode of transmission of rabies*
4. *Explain the epidemiology of rabies*
5. *Describe the pathophysiology of rabies*
6. *Identify the clinical manifestations of rabies*
7. *Describe the most commonly used method for the diagnosis of rabies*
8. *Make a diagnosis of rabies*
9. *Refer people who were bitten by rabied animals to hospitals for post exposure prophylaxis*
10. *Design appropriate methods of prevention and control of rabies*

Definition: Rabies in an acute central nervous system disease that is caused by rabies virus, an RNA virus, which is transmitted by infected secretions.

***Etiology*: -** The rabies virus is a single stranded RNA virus which belongs to the rhabdovirus family.

Epidemiology:

- Rabies is found in animals in most regions of the world. Source of infection could be domestic or wild animals.
- Human infection occurs through contact with un-immunized domestic animals or exposure to wild animals in the periphery. Humans are occasionally infected by wild animals like foxes and bats, but domestic dogs are responsible for more than 90% of human cases worldwide.
- The incubation period of rabies is very variable, which ranges from as early as 7 days to as late as more than one year, but the mean incubation period is 1 to 2 months.

Pathogenesis: Rabies virus enters the body through skin or mucous membrane. There is initial replication of virus at the muscles around port of entry. The virus then ascends to the CNS through the neuromuscular junction. Once in the CNS, the virus replicates in the gray

matters. The virus then passes to other organs like kidneys, salivary glands, heart, and skin, following the autonomic nervous system.

Passage of the virus into salivary gland facilitates further transmission.

Clinical manifestations:

Clinical manifestations can be divided into four stages.

- ***Prodromal stage:*** usually it lasts less than 4 days; it is manifested by fever, headache, malaise, and anorexia and vomiting.
- ***Encephalitis phase:*** starts with excitation and agitation but later there will be confusion, hallucination, aggressive behavior, muscle spasms, meningismus, opisthotonus, seizure and focal paralysis. Patients may have fever, irregular pupils, salivation, perspiration and postural hypotension.
- ***Brainstem dysfunction:*** begins soon after the encephalitis phase. There will be multiple cranial nerve deficits. Excessive salivation and inability to swallow results drooling of saliva. Hydrophobia is seen in about 50% of cases.
- ***Death:*** Patients rapidly develop coma and death is usually caused due to respiratory failure (by apnea).

Laboratory Findings: Early in the course, routine investigations are normal. Later the white cell count is usually moderately elevated, but it may as well be normal.

However, the diagnosis of rabies rests on identification of the virus or serologic tests.

Treatment

Once clinical disease appears, mortality is almost 100%. So far only 6 cases have recovered from disease in the world. Therefore anyone with history of domestic or wild animal bite should be taken seriously.

Post exposure prophylaxis: should be considered in people who had physical contact with saliva or secretions of infected animals or bitten by unprovoked animal e.g. a dog may likely have rabies. Post exposure prophylaxis of rabies includes:

- Rigorous cleansing and treatment of the wound
- Administration of rabies vaccine together with anti-rabies immunoglobulin.
- As the incubation period of rabies is variable, post exposure prophylaxis should be initiated as long as there is no clinical evidence of rabies.

Pre-exposure Prophylaxis: people who are at risk of contact with rabies like veterinarians, laboratory workers and animal handlers should receive pre exposure prophylaxis.

Reference

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Rabis virus, pages 1155-1160

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7.3. Anthrax

Learning Objective: At the end of this unit the student will be able to

1. *Define anthrax*
2. *Classify anthrax*
3. *Mention the etiology of anthrax*
4. *Describe the mode of transmission of anthrax*
5. *Explain the epidemiology of anthrax*
6. *Describe the pathophysiology of anthrax*
7. *Identify the clinical manifestations of anthrax*
8. *Describe the most commonly used tests for the diagnosis of anthrax*
9. *Make a diagnosis of anthrax*
10. *Treat anthrax at the primary care level*
11. *Design appropriate methods of prevention and control of anthrax*

Definition: anthrax is an infection that is caused by *Bacillus anthracis.* It mainly affects herbivorous animals but humans are infected by contact with the causative agent from infected animals, by contact, ingestion or inhalation.

Etiology: *Bacillus anthracis* is a large, aerobic, spore-forming, gram-positive rod, which is encapsulated and non-motile.

Epidemiology: Anthrax is more common in herbivorous animals like cattle, sheep and goats. They are infected while grazing on contaminated grass. Humans may acquire anthrax from agricultural sites through contact with animals like butchering and feeding or industrial sites through exposure to contaminated hides, wool or bones.

Pathogenesis:

- Cutaneous anthrax is initiated when spores of *B. anthracis* are introduced through abrasions of the skin or insect bite.
- Inhalation anthrax is acquired by directly inhaling the agent to the alveoli.
- Gastrointestinal form usually occurs after ingestion of raw or partially cooked meat that is contaminated.

B. anthracis goes to the blood stream and replicates rapidly. It is resistant to phagocytosis. It also produces anthrax toxin, which causes edema and inhibition of polymorphonuclear leucocyte function. Moreover, it causes release of cytokines, shock and death.

Clinical Manifestations

About 95% of anthrax is cutaneous form. 5% is inhalation, and that of gastrointestinal (GI) is very rare. GI form is more common in areas where raw meat is ingested.

Cutaneous anthrax:

- The lesions are more common on exposed areas like face, neck and extremities.
- In the beginning, a small red macule develops within days. This will become papular and pustular which then forms a central necrotic ulcer (black eshcar) with surrounding edema; it is painless.
- Usually there is associated painful regional lymphadenopathy and fever is uncommon.
- Most patients recover spontaneously but about 10% develop progressive infection, bacteremia, high grade fever and rapid death.

Inhalational anthrax (wool sorter's disease):

- This form resembles severe viral respiratory disease and thus diagnosis is difficult.
- This form may be used as biological warfare.
- Within 3 days of infection patients develop fever, dyspnea, stridor, hypoxemia, hypotension and may die within 24 hours once patients become symptomatic.

Gastrointestinal anthrax: Patients may have nausea, vomiting, abdominal pain, bloody diarrhea, and fever; they may develop ascites.

Treatment

Cutaneous anthrax

- Can be treated with crystalline penicillin 2 million units 6 hourly until edema subsides then oral penicillin for 7-10 days.
- For allergic patients, ciprofloxacin, erythromycin, TTC or chloramphenicol may be given.
- Wound should be cleaned, debrided and dressed.

Inhalation or GI form

- Should be treated with high dose penicillin 8-12 million units per day, divided into 4-6 doses.

Mortality rate

- Cutaneous Anthrax is 10-20%, for and almost.
- GI Anthrax can 50%
- Inhalational anthrax 100% for

Prevention:

- Mass vaccination of animals
- Avoiding feeding on infected cattle
- Proper disposal of dead animals and
- Keeping personal hygiene.

Reference:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Anthrax , pages 1280-1-83

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6.4 Brucellosis

Learning Objective: At the end of this unit the student will be able to

1. *Define brucellosis*
2. *List the etiologies of brucellosis*
3. *Describe the mode of transmission of brucellosis*
4. *Explain the epidemiology of brucellosis*
5. *Describe the pathophysiology of brucellosis*
6. *Identify the clinical manifestations of brucellosis*
7. *Describe the most commonly used tests for the diagnosis of brucellosis*
8. *Make a diagnosis of brucellosis*
9. *Treat brucellosis at the primary care level*
10. *Design appropriate methods of prevention and control of brucellosis*

Definition: Brucellosis is a zoonotic disease caused by *Brucella species*, which is characterized by remittent type of fever and multi-organ involvement. It is transmitted to humans from infected animals.

Etiology*:* It is caused by four different types of Brucella. They are small aerobic gram-negative bacilli; they are non-motile and facultative intracellular parasites.

- Brucella melitensis (the most common and most virulent type) acquired from goats, sheep and camels.
- Brucella abortus from cattle
- Brucella suis from hogs
- Brucela canis from dogs

Epidemiology:

- It is found worldwide, but the true incidence is not known. In communities where brucellosis is endemic, it occurs in children and family members of infected persons are at risk. Commonly affected are farmers, meat-processing workers, veterinarians, and laboratory workers.

- Brucella organism is transmitted commonly through the ingestion of untreated milk or milk products; raw meat and bone marrow have been implicated. But it can also be transmitted by inhalation from close contact with animals.

Pathogenesis: In the blood Brucella is ingested by polymorphonuclear leukocytes and macrophages but they resist intracellular phagocytosis. Severity of the disease is largely determined by the outcome of pathogen-phagocyte interaction. The organisms multiply, reach blood stream via lymphatics, and then reside in different organs, the liver, spleen, bones, kidneys, lymph nodes, heart valves, nervous system and testes. In infected organs there will be inflammatory responses or noncaseating granulomas. Serum IgM will appear within a week and later IgG and IgA will develop.

Clinical manifestations and complications:

- Brucellosis is a systemic illness and its manifestations mimic other febrile illnesses.
- The incubation period is about 1-3 weeks. The illness may begin suddenly or it could be gradual.
- The most common symptoms are fever, chills, diaphoresis, headache, myalgia, fatigue, anorexia, joint and low back-pain, weight loss, constipation, sore throat and dry cough.
- Patients may look well with no findings or may exhibit physical findings related to the organ affected.
- Fever of brucellosis has no distinctive features but it occurs in late afternoons or evenings.
- Patients may have reactive asymmetric polyarthritis involving larger joints; and lumbar vertebral osteomyelitis.
- Cardiovascular complications of Brucellosis include endocarditis, myocarditis, pericarditis, thrombophlebites and pulmonary embolism.
- Brucella can have respiratory manifestations like sore throat, tonsillitis, dry cough and even pneumonia and lung abscess.
- Gastrointestinal manifestations are generally mild and include nausea, vomiting, abdominal pain and diarrhea; there is hepatosplenomegaly in about 15-20% of patients.
- Patients may have genitourinary infection and present with epididymoorchitis, prostatitis, amenorrhea, tubo-ovarian abscess, salphingitis, acute pyelonephritis and glomerulonephritis.

- Nervous system involvement is uncommon but when involved patients may have meningitis, meningoencephalitis, brain abscess, hemiplegia and cranial nerve deficit.
- Other manifestations are conjunctivitis, retinopathy, skin involvement, abortion, anemia, leukopenia and thrombocytopenia.

Diagnosis

The combination of history of exposure, clinical features and significantly raised levels of Brucella agglutinin confirms the diagnosis of active brucellosis.

Treatment

- The combination of doxycycline and aminoglycoside (gentamicin, or streptomycin) for 4 weeks followed by the combination of doxycycline and rifampin for 4 to 8 weeks is the most effective treatment modality.
- Alternative regimen is combination of doxycycline and rifampin given for 8 to 12 weeks.
- Patients with serious illness and complication need admission for treatment with intravenous medications and possible surgical intervention.

Prevention - Immunization of animals, boiling or pasteurizing milk are important in preventing the disease.

Reference:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Brucellosis , 914-917

CHAPTER TWO
DISEASES OF THE RESPIRATORY SYSTEM

1. Common Symptoms of Respiratory System

Learning Objective: At the end of this unit the student will be able to

1. *List the common symptoms of diseases of the respiratory system*
2. *Characterize each of the symptoms*
3. *Describe the pathophysiology of each symptom*
4. *Identify disease conditions associated with each symptom*
5. *Describe the most commonly used investigations of the respiratory system*

Cough

Cough is an explosive expiration that provides a protective mechanism for clearing the trachiobronchial tree of secretions and foreign material. However, when excessive, it is one of the commonest presentations (complaint).

As a protective mechanism against foreign or noxious material, cough can be initiated by a variety of airway irritants, which enter the trachiobronchial tree by inhalation (smoke, dust, fumes) or by aspiration (upper airway secretions, gastric contents, foreign bodies).

Any disorder resulting in inflammation, constriction, infiltration, or compression of airways can be associated with cough. Inflammation commonly results from airway infections, ranging from. Some causes of cough are:

- Inflammation-infection (viral ,bacterial etc) , bronchitis , bronchiectasis, asthma etc
- Constriction - asthma (it is reversible)
- Infiltration – tuberculosis, neoplasm, granuloma, or sarcoidosis

Examples of parenchymal lung disease potentially producing cough include pneumonia, interstitial lung disease, and lung abscess.

Patients with congestive heart failure may have cough, because of interstitial edema.

Approach to the Patient with cough

A detailed history frequently provides the most valuable clues for etiology of the cough. Particularly important questions include:

- Is the cough acute or chronic? Factors influencing it?
- Were there associated symptoms suggestive of a respiratory infection?
- Is it seasonal or associated with wheezing? Dyspnea?
- Is there nasal discharge or gastroesophageal reflux (heartburn)?
- Is there fever or sputum? If sputum is present, what is its character?
- Does the patient have any associated disease or risk factors for disease (e.g. Cigarette smoking, risk for HIV, environmental exposures eg. pollution)?

The general physical exam may point to a non-pulmonary cause of cough, such as heart failure, malignancy, or AIDS.

- Auscultation of the chest may demonstrate: inspiratory stridor (indicative of upper airway disease), respiratory wheezing (indicating lower airway disease) or inspiratory crepitations (process involving the pulmonary parenchyma, such as interstitial lung disease, pneumonia, tuberculosis or pulmonary edema).

Complications of cough: may precipitate syncope, fracture of the ribs etc

Definitive treatment of cough depends on determining the underlying cause and then initiating specific therapy. Different cough suppressants can be used in addition to specific therapy to decrease the duration of cough.

Chest Discomfort/pain

Chest discomfort is one of the most frequent complaint for which patients seek medical attention. There is little relation between the severity of chest discomfort and the gravity of its cause.

Causes of Chest Discomfort

Pleuritic chest pain – It is usually a brief, sharp, knifelike pain that is precipitated by inspiration or coughing. It is very common and generally results from inflammation of parietal pleura. Typical example is pneumonia.

Myocardial ischemia:

- Angina pectoris is usually described as a heaviness, pressure, squeezing or sensation of strangling or constriction in the chest, but it also may be described as an aching or burning pain or even as indigestion.
- Typically, angina pectoris develops during emotion or physical exertion. The pain typically resolves within 5-30 minutes. The pain is more prolonged in myocardial infarction (MI).

Chest pain due to pericarditis:-

- The pain arises from parietal pericardium and adjacent parietal pleura. Infectious diseases and inflammation are the main causes of pain.
- Pericarditis can cause pain in several locations like the tip of the shoulder and the neck more often the pain is located in the anterior part of the chest and is relieved by bending forward; but pain may also be in the upper part of abdomen or at corresponding region of the back.
- Pericardial pain commonly has a pleuritic component; i.e. it is aggravated by cough and deep inspiration, because of pleural irritation. Sometimes there may be steady substernal discomfort that mimics acute myocardial infarction.

Vascular causes of chest pain: –

- Pain due to acute dissection of the aorta usually begins abruptly, reaches an extremely sever peak rapidly.
- It is felt in the center of the chest and/ or the back, lasts for hours and requires unusually large amounts of analgesics for relief of pain. Pain is not aggravated by changes in position or respiration. Usually there is associated low blood pressure.

Chest pain due to pulmonary embolism:-

- The pain resulting from pulmonary embolism may resemble that of acute MI, because in massive embolism pain is located substernally.
- In patients with smaller emboli, pain is located more laterally, is pleuritic in nature, and sometimes is associated with hemoptysis.

Gastrointestinal causes of chest discomfort:-

- Esophageal pain commonly presents as a deep thoracic burning pain, which is the hallmark of acid-induced pain. Esophageal spasm has acute pain that may be indistinguishable from MI.

- Other diseases like PUD, biliary disease, pancreatitis, and cholecystits may present as chest discomfort or pain.

Emotional cause of chest pain - Usually, the discomfort is experienced as a sense of "tightness", sometimes called "aching". It is confused with myocardial ischemia. Ordinarily, it lasts for half an hour or more. There is usually associated emotional strain or fatigue.

Hemoptysis; is defined as expectoration of blood from the respiratory tract, which could be scanty and mixed with sputum or large amount of frank blood. Massive hemoptysis is defined as expectoration of >600 ml of blood in 24 hours. Hemoptysis can have different causes. Some of the causes are:

1) Tracheobronchial source

- Neoplasm
- Bronchitis , Bronchiectasis
- Foreign body
- Airway trauma

2) Pulmonary parenchymal source

- Pneumonia, tuberculosis
- Lung abscess
- Lung congestion

3) Primary vascular source

- Mitral stenosis
- Pulmonary embolism

4) Sources other than the lower respiratory tract

- Upper airway (nasopharyngeal) bleeding
- GI bleeding

❖ Tuberculosis and pneumonia are the commonest causes of hemoptysis in developing countries. But bronchitis and bronchogenic ca are common in developed regions. Up to 30% of patients may not have identifiable cause even after complete investigation.

Approach to the patient with hemoptysis

History:

- Blood streaked, mucopurulent sputum suggests bronchitis.
- If it is associated with fever pneumonia should be suspected.
- If sputum smell is putrid, lung abscess is likely.
- Hemoptysis that occurs suddenly with chest pain and dyspnea suggests pulmonary embolism.
- Previous history of renal disease, SLE, or malignancy is all important for suggesting DDX.

Physical examination: may reveal

- Pleural friction rub, Localized or diffuse crackles → lung paranchymal damage.
- Wheezing →Airflow obstruction (chronic bronchitis).
- Cardiac examination may reveal pulmonary hypertension, mitral stenosis or heart failure

Diagnostic evaluation :

- Chest X-ray which may show mass lesion suggestive of bronchiectasis, pneumonia.
- Sputum examination for Gm and AFB stain.
- CBC, coagulation profile, urine analysis,
- BUN and creatinine and
- If possible bronchoscopy is useful in localizing and managing the site of bleeding

Treatment: the rapidity of bleeding and its effects on gas exchange determine the urgency of management.

- If there is only blood streaking sputum with mid hemoptysis, first establish diagnosis. Put the patient at rest and Giving cough suppressant may help to subside the bleeding
- If massive hemoptysis urgent treatment is necessary to stop bleeding and patients should be referred to a hospital. Massive hemoptysis may require endotracheal intubation and mechanical ventilation. If the bleeding side is known position the patient so that the source of bleeding is placed in dependent position to protect suffocation of the unaffected lung.

2. Upper Respiratory Tract Infections

Learning Objective: At the end of this unit the student will be able to

1. *Define upper respiratory infections*
2. *List the etiologies of upper respiratory infections*
3. *Describe the mode of transmission of upper respiratory infections*
4. *Explain the epidemiology of upper respiratory infections*
5. *Describe the pathophysiology of upper respiratory infections*
6. *Identify the clinical manifestations of upper respiratory infections*
7. *Describe the most commonly used method of diagnosis of upper respiratory infections*
8. *Make a diagnosis of upper respiratory infections*
9. *Give supportive therapy at the primary care level*
10. *Design appropriate methods of prevention of upper respiratory infections*

2.1 The Common Cold (Acute coryza)

It is an acute, usually afebrile, viral infection of the respiratory tract, with inflammation in any or all airways, including the nose, paranasal sinuses, throat, larynx, and often trachea and bronchi.

Etiology - Many viruses cause the common cold including Picornavirus (rhinoVirus), Influenza and parainfluenza viruses, Respiratory syncytial virus, Corona- and adeno virus group.

Infections may be facilitated by excessive fatigue, emotional distress, or allergic naso pharyngeal disorders and during the mid-phase of the menstrual cycle.

Symptoms and signs - onset is abrupt after a short (1 to 3 days) incubation period. Illness generally begins with nasal or throat discomfort followed by sneezing, rhinorrhea, and malaise. The disease is afebrile and pharyngitis is usually present. Nasal secretions, watery and profuse during 1st or 2nd day of symptoms, become more mucous and purulent. Hacking cough associated with scanty sputum often lasts into the 2nd week. When no complications occur, symptoms normally resolve in 4 to 10 days.

Diagnosis- Symptoms and signs are nonspecific. Bacterial infections, allergic rhinorrhea, and other disorders also cause upper respiratory tract symptoms at onset. Differentiation depends on the season and the course of the Symptoms. Fever more severe symptoms usual indicate influenza.

Prophylaxis - Immunity is virus type-specific. Because of numerous types and strains of known viruses causing URT, it is difficult to produce a useful vaccine.

Treatment

- A Warm, comfortable environment and measures to prevent direct spread of infection are recommended for all persons.
- Antipyretics and analgesics are given to control fever and malign.
- Nasal decongestants are used if patients have nasal congestion. Steam inhalation is also used in nasal congestions to help mobilize secretions and relieve chest tightness.
- Treat persistent cough with cough suppressants.
- Ascorbic acid or high doses of citrus juices have no scientific benefit.
- Antibiotics are not effective against viruses, so they are not recommended unless a specific bacterial complication develops.

2.2 Influenza

Influenza is a specific acute viral respiratory disease characterized by fever, coryza, cough, headache, and malaise and inflamed respiratory mucous membranes. It usually occurs as an epidemic in rainy seasons.

Etiology*:* It is caused by influenza viruses, which are classified as orthomyxovirus. There are types A, B & C

Epidemiology:

- Influenza type A virus is the most frequent single cause of clinical influenza; other causes include influenza B, paramyxovirus, pneumonia-virus and (rarely in adults) rhino and echoviruses.
- Spread is by person - to - person contact; airborne droplets spray infects people and contaminates articles with viruses that can transmit infection.
- Persons of all ages are affected, but prevalence is highest in school children.
- Persons at highest risk of developing severe disease are those with chronic pulmonary disease and those with valvular heart disease, pregnant women, the elderly, the very young and the bed ridden.
- Infection with influenza A is associated with significant morbidity and mortality.

Symptoms and Signs:

- During the 48-hour incubation period, transient asymptomatic viremia occurs.
- Then there is chills and fever up to 39 to 39.5 ^{0}c developing over 24 hr.

- Generalized aches and pains (most pronounced in the back and legs) appear early.
- Headache is prominent.
- Respiratory tract symptoms may be mild initially but become prominent later.
- The soft palate, posterior hard palate, and tonsillar pillars may be reddened. Usually after 2 to 3 days, acute symptoms rapidly subside and fever ends.
- Weakness, sweating and fatigue may persist for several days or occasionally for weeks.
- In severe cases, hemorrhagic bronchitis and pneumonia are frequent and can develop within hours.
- Fulminant, fatal viral pneumonia may occur and death may follow as soon as 48 hr after onset. This is usually during a pandemic caused by a new virus or in high-risk people.

Complication:

- Secondary bacterial infection of the bronchus and pneumonia. With pneumonia, cough worsens and purulent or bloody sputum is produced. Crepitations can be detected over affected segment.
- Encephalitis, myocarditis, and myoglobinuria may occur as complications of influenza, usually during convalescence.

Diagnosis:

- Clinical influenza is a common experience and can easily diagnosed. Chest examination is usually normal in mild cases and may look like common cold. Pulmonary symptoms may be similar to those of bronchitis or atypical pneumonia. Fever and severe constitutional symptoms differentiate influenza from the common cold
- The leukocyte count is normal in uncomplicated cases.
- Isolating the virus can make specific diagnosis of influenza. Serologic tests are also used.

Prognosis: Recovery is the rule in uncomplicated influenza. Viral pneumonia may cause death.

Prophylaxis: Vaccines that include the prevalent strains of influenza viruses effectively reduce the incidence of infection. Amantadine 100mg orally bid (for adults) can be used prophylactically against influenza A.

Treatment:

- Amantadine has a beneficial effect on fever and respiratory symptoms if given early in uncomplicated influenza.

- Basic treatment for most patients is symptomatic with bed rest, antipyretics, nasal decongestants & steam inhalation.

2.3 Acute Bronchitis

It is an acute inflammation of the tracheobronchial tree, generally self-limiting and with eventual complete healing and return to normal function. It could be caused by infections or irritants.

Etiology:

- *Acute infectious bronchitis* is often part an acute upper respiratory tract infection (URTI). It may develop after a common cold or other viral infection of the nasopharynx, throat or tracheobronchial tree, often with secondary bacterial infection.
- *Acute irritative bronchitis* is caused by various mineral and vegetable dusts, volatile solvents, tobacco or other smoke.

Symptoms and signs:

- Acute infectious bronchitis is often preceded by symptoms of URTI, coryza, malaise, chilliness, slight fever, back and muscle pain and sore throat.
- The onset of cough usually signals onset of bronchitis. Cough is initially dry but progresses to be productive. Purulent sputum suggests bacterial superinfection.
- In uncomplicated case, fever to 38.8^0c may be present upto 3-5 days, following which acute symptoms subside (though cough may continue for several weeks).
- Persistent fever may suggest complication like pneumonia.
- Pulmonary signs are few in uncomplicated acute bronchitis. Scattered rhonchi and wheezes may be heard, as well as occasional crepitations at the bases. Serious complications are usually seen only in patients with an underlying chronic respiratory disorder.

Diagnosis:

- It is usually based on the symptoms and signs.
- Chest X-ray is taken only to rule out serious conditions like pneumonia.
- In persons who do not respond to antibiotics, gram stain and sputum culture is necessary.

Treatment:

- General Management
- Rest until fever subsides.
- Oral fluids should be taken more:- this facilitates sputum expectoration.

- Antipyretics and analgesics (like aspirin or paracetamol) are given if there is fever or myalgia.
- Symptomatic treatment of cough may shorten the duration of cough.
- Specific Treatment
- Antibiotics should be given when purulent sputum and persistent fever are present. TTC or ampicillin can be given for 7 – 10 days.

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3. Pneumonia

Learning Objective: At the end of this unit the student will be able to

1. *Define Pneumonia*
2. *List the etiologic agents of Pneumonia occurring in different settings*
3. *Describe the mode of transmission of Pneumonia*
4. *Understand the epidemiology of Pneumonia.*
5. *Describe the pathophysiology of Pneumonia*
6. *Identify the clinical manifestations of Pneumonia*
7. *List the complications of Pneumonia*
8. *Describe the most commonly investigations for the diagnosis of Pneumonia*
9. *Make an accurate diagnosis of Pneumonia*
10. *Manage most cases of Pneumonia appropriately*
11. *Refer complicated cases of Pneumonia*

Pneumonia is an acute infection of lung parenchyma including alveolar spaces and interstitial tissue.

- Involvement may be confined to an entire lobe -Lobar pneumonia
- A segment of a lobe-Segmental or lobular pneumonia
- Alveoli contiguous to bronchi - Bronchopneumonia
- Interstitial tissue - Interstitial pneumonia

These distinctions are generally based on x-ray observations.

Predisposing factors for pneumonia include:-

- Preceding respiratory viral infections
- Alcoholism
- Cigarette smoking
- Underlying diseases such as Heart failure, COPD
- Age extremes
- Immunosuppressive therapy and disorders
- Decreased consciousness, comma , seizure etc
- Surgery and aspiration of secretions

The usual mechanisms to develop pneumonia are either to inhale droplets small enough to reach the alveoli, or to aspirate secretions from the upper airways. Other means include hematogenous dissemination, via the lymphatics, or directly from contiguous infections.

Microbial Pathogen that cause Pneumonia: *depend on the setting in which pneumonia is acquired*

1. ***Community-acquired pneumonia***
    - *Streptococcus pneumoniae (* pneumococcal pneumonia) commonest cause
    - *Mycoplasma pneumoniae*
    - *Chlamydia pneumoniae*
    - *Haemophilus influenza*
    - *Oral anaerobic bacteria*
    - *Staphylococcus aureus*
    - *Legionella pneumophila*
    - *Mycobacterium tuberculosis*
2. ***Aspiration pneumonia:*** This occurs when large amount of oropharyngeal or gastric contents are aspirated into the lower respiratory tract. Aspiration occurs more frequently in patients with:
    - Decreased level of consciousness (alcoholism, seizure, strokes or general anesthesia)
    - Neurologic dysfunction of oropharynx and swallowing disorders.
    - People with periodontal disease are affected more.

    Common Etiologic agents of Aspiration pneumonia: It is often polymicrobial
    - *Anerobic organisms in the oral cavity*
    - *Enterobateriacae*
    - *S. pneumoniae*
    - *S.aureus*

    Patients present with cough and foul smelling sputum. The cough may be chronic forming lung abscess and may resemble TB. There will be signs of cavity on physical exam and CXR. It is treated with crystalline penicillin and metronidazole IV for several weeks if lung abscess develops.
3. ***Community acquired Pneumonia in Immunocompromised hosts:***

    Immunocompromised hosts such as transplant recipients, HIV infected patients, and patients on Chemotherapy etc. are prone to develop pneumonia. The etiologic agents are

- Common bacterial causes of CAP : *St. Pnumoniae , H.influenzae, Mycoplasma*
- Gram negative organisms : enterobacteriaceae
- Funguses such as Pneumocystis carinii (jerovecii), *C. neoformans , Histoplasmosis , Aspergillus*
- *Mycobaterium tuberculosis*
- *Viruses : HSV , CMV*

4. ***Hospital-acquired pneumonia:*** a patient is said to have hospital acquired pneumonia if the symptoms begin 48 hours after hospital admission and not incubating at the time of admission. Common organisms that cause hospital-acquired pneumonia are:-
   - Gram-negative bacilli including *Pseudomonas aeroginosa*, *K.pneumoniae*
   - *Staphylococcus aureus (may ne drug resistant)*
   - *Oral anaerobes.*

Clinical Presentation of community acquired pneumonia

- Community acquired pneumonia can have typical or atypical presentations. This classification is less distinct but it may have diagnostic value. More commonly patients have "typical" presentation and it is mainly caused by *S.Pneumonae*. But other organisms like *H. influenza* and oral flora can be causes.
- Pneumonia is often preceded by a URTI.

The "typical" Community acquired pneumonia: is characterized by:-

- Sudden onset with a single shaking chill. This is followed by high grade fever (upto 40.5^0c)
- Cough productive of purulent, blood streaked or rusty sputum
- Pleurtic chest pain on the involved side worsened during inspiration and coughing
- Daphnia (shortness of Breath)
- Headache , myalgia , arthralgia and fatigue

Physical findings

- The Patient will have tachycardia (pulse 100 to 140/min)and tachypnea (RR > 20/min).
- There will be pulmonary signs of consolidation (lobar pneumonia), which are
  - Increased tactile fremitus and vocal fremitus , dullness on percussion
  - Bronchial breath sound, egophony, wispering pectoriloquy, crackles and pleural friction rub.

The "atypical" pneumonia present with:

- Atypical" pneumonia is usually caused by *M. pneumoniae*, *C.pneumoniae*, *oral anaerobes* and *P. carinii* (usually in HIV patients), as well as S. Pneumoniae. Some viruses like influenza virus, Varicella zoster virus and cytomegalovirus may cause "atypical" pneumonia. Tuberculosis could also present in this form.
- More gradual onset of symptoms, dry cough, shortness of breath.
- Prominence of systemic symptoms like headache, malign, fatigue, nausea, vomiting and diarrhea.
- Chest findings on physical examination are minimal even though X-ray changes are marked.

Complications:

- ***Local***: Parapneumonic effusion or pus in the pleural space (empyema).
- ***Distant complications***: include septic arthritis and meningitis. Pneumonia can progress to sepsis, sometimes with septic shock.

Laboratory findings:

1) ***CBC***: leucocytosis with increased neutrophils is seen in most cases.
2) ***Gram stains from sputum*** may show a predominant pathogen like Gram-positive diplococci.
3) ***Chest x-ray shows*** pulmonary infiltrates or homogeneous opacity indicating lobar pneumonia. Very early in the course, it may be normal.

Diagnosis:

- Pneumonia should be suspected in patients with acute febrile illness, associated with chest pain, dyspnea and cough.
- Presumptive diagnosis can be made from history, changes on chest x-ray, blood and sputum culture and sputum Gram stains. An absolute diagnosis requires demonstration of *S. pneumoniae or other etiologic agents* in pleural fluid, blood, lung or transtracheal aspirate.

Prognosis: The overall mortality rate is low, if treated early. Factors that herald a poor prognosis include the following:-

- Extremes of age, especially < 1 yr or >60yrs,
- Positive blood culture
- Involvement of more than one lobe
- Peripheral WBC < 5000/ml

- Presence of associated diseases (e.g. cirrhosis, CHF, immunosuppression)
- Development of extrapulmonary complications like meningitis and endocarditis.

Management:

Mild form of CAP

Patients with uncomplicated "typical" pneumonia can be treated at OPD

- Amoxicillin 500 mg PO TID or Ampicillin 500 mg PO QID for 7 to 10 days OR.
- Procaine penicillin 600,000 IU IM every 12 hrs.

If "atypical" pneumonia is suspected,

- Erythromycin 500 mg PO QID for 7-10 days or Doxycycline100 mg PO BID

Supportive Therapy: Patients should also get bed rest, adequate fluids and analgesics for pleuritic chest pain and fever.

Response – In mildly ill patients who are treated early, fever subsides in 24 to 48 hrs. Others may require 4 days to respond.

- If Patients are allergic to penicillins, cephalosporins, erythromycin, and clindamycin can be given. TTC are less predictable and should not be used in seriously ill patients.
- If a patient does not improve, the following factors should be considered:
  - Wrong etiologic diagnosis
  - Adverse drug reaction
  - Far advanced case or superinfection
  - Inadequate host defenses due to associated condition
  - Non-compliance to the drug regimen in outpatients
  - Antibiotic resistance of the strain and
  - Complications like empyema requiring drainage, or metastatic foci of infection requiring higher doses (e.g. meningitis, endocarditis or septic arthritis).

- Persistent cough and infiltration on chest x-ray for more than 6 weeks after therapy suggests possibility of an underlying bronchogenic neoplasm or tuberculosis.

Severe forms of CAP

If patients are seriously ill they should be admitted and treated as inpatient.

Criteria for Hospitalization of patients with Pneumonia are:

1) *Respiratory rate of >28/min (Tachypnea) tachycardia >140/min*
2) *Systolic blood pressure <90mm Hg (hypotension*
3) *Hypoxemia (arterial PO_2 < 60mm Hg) while breathing room air or O_2 saturation < 90 %*

4) *New onset of confusion or impaired level of consciousness .*
5) *Unstable /Significant co-morbidity (e.g. Heart faiure , uncontrolled diabetes, Chronic Renal insufficiency ,alcoholism , immunosuppresion)*
6) *Multilobar pneumonia is Hypoxemia is present*
7) *Pleural effusion and with analysis showing characteristics of complication*

Other conditions in which inpatient management may be advisable

- *Elderly patient >65 yrs of age*
- *Leukopenia <5000 WBC/ml*
- *Pneumonia caused by St. aureus or Gram negative bacilli*
- *Suppurative complications e.g. empyema, arthritis, meningitis, endocarditis*
- *Failure of Outpatient treatment*
- *Inability to take oral medication or persistent vomiting*

Management of CAP

Supportive management

- Ensure adequate oxygenation to patients with cyanosis, significant hypoxemia, sever dyspnea, circulatory disturbance or delirium.
- Patients should be well hydrated
- Fever and pain should be managed

Antibiotic Therapy

- Admitted patients should be started on antibiotics empirically
- High dose of crystalline penicillin 3-4 million IU IV every 4-6 hours
- Alternatives are Ceftriaxone 1gm IV daily or 2X /day or Ampicillin 500 mg IV QID Or Cefotaxime
- In severely ill patients erythromycin or a flouroquinolone can be added.
- Choice of Antibiotics may be modified based on culture and sensitivity results, if available.
- If the patient improves, IV treatment can be changed to oral after 3-4 days to complete a 7-10 days course.

Prevention

- Cessation of smoking and alcoholism
- Vaccines : Influenza an Pneumococcal vaccines (available in developed countries)

Pneumonia in the Compromised Host

- Immunocompromised hosts include patients with AIDS, acute leukemia, cancer chemotherapy, diabetes, sickle cell disease, Hodgkin's disease, and corticosteroid treatment.
- The potential pathogens in compromised hosts are many, as it has been stated above.
- Pathogens like Streptococcus pneumonia, which cause pneumonia in immunocompetent people, are still responsible for the majority of pneumonia in compromised patients.

Diagnosis:

- Sputum examination and culture are used but they are not specific.
- Transtracheal aspirate, bronchoscopy and biopsy have high accuracy; however these are done only in specialized hospitals.
- High index of suspicion from clinical presentation is important to diagnose pneumonia in immunocompromised hosts.

Treatment:

- Acutely ill patients who have suspected bacterial infections are often treated with antibiotics selected on the basis of probabilities and the findings with sputum gram stain and culture. Later treatment is adjusted on the basis of more definitive diagnostic evaluation.
- In patients with HIV infection and “atypical” pneumonia, PCP should be considered and treated with high dose of co-trimoxazole (3 tablets every 6 hours for 3 weeks) if clinically considered.

Hospital acquired Pneumonia (HAP)

The definition of HAP includes the presence of a new or progressive infiltrates of Chest X-ray , plus at least two of the following

- Fever >37.8 ^{o}C
- Leukocytosis > 10,000/mm^{3}
- Production of purulent sputum

Other findings: dyspnea, hypoxemia and chest pain

Treatment

Antibiotics: Should be initiated empirically which latter on may be modified based on culture and sensitivity result.

The selection of drugs should be guided by an understanding of local patterns of antibiotics resistance

Antibiotics should cover at least gram negatives and *S. aureus*

- Ceftriaxone 1gm IV daily or BID plus Cloxacillin or meticillin Or
- Levofloxacin 500 mg IV /day

When resistant organisms are suspected

- Cefotaxime 750 mg IV TID plus Vancomycin 1gm IV BID

Prevention

- Strict hand washing protocols by health care providers
- Extubate an entubated patient as soon as the patient is stable
- Remove NG tubes when the patient is stable
- Proper aseptic handling of IV lines

References:

4) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Pneumonia, pages 1528-1540

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4. Bronchial Asthma

Learning Objective: At the end of this unit the student will be able to

1. *Define bronchial asthma*
2. *Understand the epidemiology of bronchial asthma.*
3. *Describe the etiology of bronchial asthma.*
4. *Understand the pathophysiology of bronchial asthma .*
5. *Identify the clinical manifestations of bronchial asthma.*
6. *List the signs of severity of bronchial asthma.*
7. *Make an accurate diagnosis of bronchial asthma.*
8. *Manage most cases of bronchial asthma.*
9. *Refer complicated cases of bronchial asthma.*

Definition: Bronchial asthma is defined as chronic inflammatory disease of airways characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli. It is associated with widespread airway obstruction that is reversible (but not completely in some patients), either spontaneously or with treatment

Epidemiology:

- Asthma is a common disease The prevalence of asthma is rising in different parts of the world.
- It can occur at any age; but it usually starts early in life. About 50% of patients develop asthma before the age of 10 and another 35% before the age of 40.
- Males are affected twice as common as females in early life; this sex difference equalizes by age 30. Most cases of asthma are associated with personal or family history of allergic disease such as eczema, rhinitis and urticaria.

Etiology Asthma is a heterogeneous disease and genetic (atopic) and environmental factors such as viruses , occupational exposure and allegens contribute to its initiation and continuance . Atopy is the single most important risk factor for asthma

Asthma can be classified in to 3 types Allergic (atopic) , Nonallergic (idiosyncratic) and Mixed

Table II-4-1 Comparison of the two major types of Asthma

	Allergic (Atopic) asthma	***Non Allergic (idiosyncratic)***
Age of onset	Early in life	Late in life
Family or personal history of allergy: rhinitis , urticaria eczema	Present	Absent
Skin test with intradermal injection of allergens	Positive wheal-and -flare skin test	Negative skin test
Serum IgE level	Elevated	Normal
Response to inhalation provocative test	positive	Negative

Many patients have disease that doesn't fit into either of the 2 categories, but instead fall into a mixed group with some features from each group. In general asthma which has its onset early in life tends to have strong allergic component, where as asthma that develops late in life tends to be nonallergic or to have mixed etiology.

Factors important for the genesis of asthma

- ***Genetic factors***
    - Asthma has strong genetic predisposition or familial tendency

Stimuli that incite Asthma

- ***Allergens :*** Seasonal allergens such as pollen green
    - Non seasonal animal feathers , dust mites , molds
- ***Pharmacologic stimuli***: Aspirin , Tatrazin (coloring agent), Beta blockers such as Propranolol etc
- ***Environmental and air pollution***: in industrial and heavily populated areas. The common pollutants are ozone, nitrogen dioxide and sulfur dioxide.
- ***Infections***: Respiratory infections are the most common of the stimuli that evoke acute exacerbation of asthma. Respiratory viruses are the major factors.

- ***Exercise: is*** a very common precipitant of acute episodes of asthma
- **Emotional stress:** psychological factors can worsen or ameliorate asthma

Pathophysiology:

Asthma results from a state of persistent subacute inflammation of the airways. The airways obstruction in asthma is due to a combination of factors. The cells thought to play important part in the inflammatory response are mast cells, eosinophils, lymphocytes and airway epithelial cells. These cells release inflammatory mediators which may result

- Bronchoconstriction (spasm of airways smooth muscles)
- Vascular congestion and edema of airways mucosa
- Increased mucus production
- Injury and desquamation of the airways epithelium and impaired muco-ciliary transport

Symptom and Signs

- The symptoms of each asthmatic patient differ greatly in frequency and degree.
- Some asthmatics are symptom free, with an occasional episode that is mild and brief; others have mild coughing and wheezing much of the time, punctuated by severe exacerbations of symptoms following exposure to known allergens, viral infection, exercise etc. Psychological factors particularly those associated with crying, screaming or hard laughing may precipitate symptoms.
- An attack usually begins acutely with paroxysms of wheezing, coughing, and shortness of breath, or insidiously with slowly increasing manifestations of respiratory distress.
- The asthmatic first notices dyspnea, tachypnea, cough and tightness in the chest and may even notice audible wheezes.

On physical examination –

- Varying degrees of respiratory distress tachypnea, tachycardia, and audible wheezes are often present.
- Dehydration may be present because of sweating and tachypnea.
- Chest examination shows a prolonged expiratory phase with relatively high pitched wheezes throughout inspiration and most of expiration.
- In more severe episodes, patients may be unable to speak more than a few words without stopping for breath.
- Cyanosis is usually a late sign of hypoxia.
- Confusion and lethargy may indicate the onset of progressive respiratory failure.

- Less wheezing (silent chest) might indicate mucous plug or patient fatigue with less airflow. And it is a sign of impending respiratory failure.
- The presence, absence, or prominence of wheezes does not correlate precisely with the severity of the attack.
- The most reliable clinical signs include the degree of dyspnea at rest, cyanosis, difficulty in speaking and use of accessory muscles of respiration. This is confirmed by arterial blood gas analysis.
- Between acute attacks, breath sounds may be normal during quiet respiration. However, low grade wheezing maybe heard at any time in some patients, even when they claim to be completely asymptomatic.

Complications during an Acute Attack of Asthma

- **Pneumothorax**: It may present as sudden worsening of respiratory distress, accompanied by sharp chest pain and on examination, hyperresonant lung with a shift of mediastinum. Chest x-ray confirms the diagnosis.
- **Mediastinal and subcutaneous emphysema** due to alveolar rupture
- **Atelectasis** due to obstruction
- **Dilated right heart chambers** (Corpulmonale) : from chronic hypoxemia and pulmonary hypertension
- **Respiratory failure**

Laboratory Findings

- ***Eosinophilia*** is a common finding.
- ***Sputum*** is tenacious, rubbery and whitish or may be yellowish; eosinophils are present in the sputum.
- ***Chest x-ray:*** varies from normal to hyperinflation. Atelectasis and pneumothorax may be seen in complicated cases.
- ***Pulmonary function tests*** are valuable in differential diagnosis and in known patients to assess the degree of airways obstruction.

Diagnosis

Asthma should be considered in anyone who wheezes. A family history of allergy, rhinitis or asthma can be elicited in most asthmatics.

Differential diagnosis includes:

- **In children**: foreign body obstruction, viral URTI involving the epiglottis (croup), and bronchiolitis (RSV infection);
- **In adults**: COPD, heart failure, endobronchial TB, and malignancies. Physical examination should search for heart failure and signs of chronic hypoxemia (clubbing). Unilateral wheezes usually indicate obstruction by foreign bodies or tumor.

Prevention of attacks

- The role of environmental factors (e.g. animal dander, dust, airborne moulds, and pollens) in acute exacerbations is clear. Allergens that can be controlled by avoidance should be eliminated.
- Nonspecific exacerbating factors (e.g. cigarette smoke, odors, irritant fumes, and change in temperature, atmospheric pressure, and humidity) should also be investigated and avoided if possible.

Treatment

General principles

- Assessing the severity of the attack is paramount in deciding management
- Bronchodilators should be used in orderly progression
- Decide when to start corticosteroids

Treatment of the Acute Attack

Mild acute asthmatic attack: Most patients can be managed as an outpatient

- Salbutamol aerosol (Ventolin®) two puffs every 20 minutes for three doses is the 1st line of treatment.
- Adrenaline 1:1000 can be given in doses up to a maximum of 0.2 ml in children and 0.3 ml in adults, repeated once or twice in 20 to 30 min (if there is no hypertension or any other contra indication).
- If the initial treatment fails, Aminophylline 250 mg IV diluted in dextrose in water should be given slowly over 10-15 minutes, once.
- If the patient does not respond to one dose of aminophylline IV, then the patient is declared to have severe asthma, and should be admitted and managed as in-patient.

In patient management

Patients who are diagnosed to have severe and life threatening asthma need in patient management. Some may even need admission to ICU.

Signs of Severity of acute asthmatic attack

1) *Tachycardia HR > 120/min , Tachypnea RR.30 min*
2) *Presence of pulsus paradoxus*
3) *Use of accessory muscles of respiration*
4) *Cyanosis*
5) *Altered state of consciousness (confusion , drowsiness)*
6) *Silent chest*
7) *Paradoxical movement of the chest and the abdomen*
8) *Presence of complications : Pneumothorax , atelectasis*
9) *Unable to finish a sentence with single breath (frequent interruption of speech to take a breath)*
10) *Laboratory parameters*
    - *PEFR < 50 % or FEV_1 < 60 %*
    - *PaO_2 < 60mmof Hg or SaO_2 < 90 %*
    - *$PaCO_2$ > 42 mmHg*

Specific drug Treatment

- ***Aminoplylline*** in doses of 1mg/kg/hr in a continuous IV infusion should be given.
- ***Corticosteroids*** should also be given IV e.g. Hydrocortisone 4mg/kg IV every 4 hrs. When the patient improves the hydrocortisone be changed to Prednisolone PO and the dosage should be tapered up on discharge.
- Patients who do not respond to aggressive drug therapy are candidates for endotracheal intubation and Mechanical Ventilation for which they should be admitted to an ICU.
- Respiratory tract infections precipitating acute asthmatic attack are predominantly viral; but if patients expectorate yellowish, green or brown sputum, antibacterial therapy is indicated. Ampicillin is the first line; alternatives are TTC, erythromycin or cotrimoxazole. Chest x-ray is taken if there is suspicion of pneumonia or complications.

Supportive Treatment

- O_2 therapy is always indicated for hospitalized patients
- Fluid and electrolyte balance requires special attention because of frequent occurrence of dehydration during acute asthmatic attack. However, over hydration may cause pulmonary edema and one should be cautious in fluid administration.
- Anxiety is common in patients with severe acute asthmatic attack. However this can be overcome when underlying hypoxia and feeling of asphyxiation is treated. Health personnel should be considerate and reassure the patient.

Maintenance Therapy for Asthma (Chronic Treatment)

Goal of Therapy: To achieve a stable, asymptomatic state with the best pulmonary function, using the list amount of medication .Drug selection is based upon the severity of illness.

Table II-4-2. Step wise approach for managing Asthma in adults

Severity	***Symptoms day/night***	***Medication***	***Alternative treatment in resource limited setting***
Mild intermittent	≤ 2 days/wk and ≤ 2 nights /month	No daily medication needed Treat when there is acute exacerbation	
Mild Persistent	> 2days /week but < 1 per day and > 2 nights/month	Low dose inhaled steroids or Cromolyn	Theophedrine tablets or Salbutamol tabs
Moderate Persistent	Daily symptoms and more than 1 night /wk	Low-medium does inhaled steroid and long acting B-agonist inhaler	Theophylline sustained release Salbutamol Tabs Prednisolone tablets (low dose
Sever Persistent	Continual daily symptoms and	High dose inhaled steroid and long acting inhaled B-	Theophylline sustained release

	frequent night symptoms	agonists and Oral steroids (if needed)	Salbutamol Tabs Prednisolone tablets (high dose) or Celestamine tabs

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Asthma, pages 1508-1515
2) Myers R. Allen , National Medical Series for independent Study (NMS) 3rd edition Medicine, Asthma, pages 75-78

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5. Chronic obstructive pulmonary diseases (COPD)

Learning Objective: At the end of this unit the student will be able to

1. *Define chronic obstructive pulmonary diseases (COPD*
2. *List the etiologies of COPD*
3. *Explain the epidemiology of COPD*
4. *Describe the pathophysiology of COPD*
5. *Identify the clinical manifestations of COPD*
6. *Outline the main differences between c. bronchitis and emphysema*
7. *Describe the most commonly used tests for the diagnosis of COPD*
8. *Make a diagnosis of COPD*
9. *Give therapy to COPD at the primary care level*
10. *Design appropriate methods of prevention of COPD*

Definition: Chronic obstructive pulmonary diseases are conditions characterized by chronic irreversible airway obstruction causing an increased resistance to outflow of air due to chronic bronchitis and emphysema. Both these diseases occur together in the same individual in a variable proportion but the manifestations of one often predominates the clinical picture.

1) ***Chronic bronchitis***: is a condition associated with excessive tracheobronchial mucus production sufficient to cause cough with expectoration of sputum for at least 3 months in a year for over 2 consecutive years.
2) ***Pulmonary emphysema***: is distension of the airspaces distal to the terminal bronchioles, accompanied by destructive changes of the alveolar septa.

Etiology

- ***Emphysema****:* Any factor leading to chronic alveolar inflammation would encourage development of an emphysematous lesion. Smoking has adverse effects on lung defenses, leading to emphysematous change. Congenital enzyme defects such as α_1-antitrypsin deficiency are also risk factors for the disease.
- ***Chronic bronchitis****:* with sufficient exposure to bronchial irritants, particularly cigarette smoke, most persons develop some degree of chronic bronchitis with signs of inflammation of the airways. In developing countries household smoke from fire wood is said to be a major contributing factor.

Prevalence:

- COPD is a major health problem especially in western societies because of the effect of cigarette smoking and aging.
- Males are affected more than females which could be attributed to the higher prevalence of smoking in males. Nowadays, the incidence of this disease in females is increasing because of the increasing smoking habit.

Pathological changes and pathophysiology

- Chronic bronchitis is characterized by hypertrophy of mucus glands in both large and small airways with thickening of walls and accompanying excess production of mucus and narrowing of airway lumen. In C. bronchitis, alveoli are often spared, and no vessel loss and lung perfusion remains normal but ventilation is very much reduced. This leads to abnormal V/Q (arteriovenous shunt) and patients usually suffer from hypoxemia (manifested with cyanosis) and acidosis, which causes pulmonary hypertension and right heart failure in the long term.
- On the other hand emphysema is characterized by destruction of alveolar septa and distension of alveoli resulting in reduced surface area and loss of vessels, the later causing reduced perfusion. Moreover, emphysema causes mucus production and airway narrowing with accompanying reduction in ventilation. This leads to retention of carbon dioxide in the blood and severe dyspnea from reduced tissue perfusion. However, these patients don't suffer from hypoxia and acidosis, and have less chance of development of pulmonary hypertension and cor-pulmonale. However, patients usually have a mixed picture of emphysema and chronic bronchitis.

Clinical features:

- COPD is thought to begin early in adult life but significant symptoms and disability do not appear until middle age.
- A mild "smoker's cough" is often present many years before onset of exertional dyspnea. Gradual progressive exertional dyspnea is the most common presenting complaint.
- Cough, wheezing, recurrent respiratory infections or, occasionally weakness, weight loss, or reduced libido may also be initial manifestations.

Physical findings: in COPD are very variable especially in early stages.

- A consistent abnormality is obstruction to expiratory airflow manifested by prolonged forced expiration (normally < 4 seconds).
- Typical findings including gross pulmonary hyperinflation, prolonged expiration during quiet breathing, pursed-lip breathing, stooped posture, and marked use of accessory muscles of respiration are seen in later stages of COPD.
- Other findings are rhonchi, diminished vesicular breath sounds, tachycardia, distant heart sounds, and decreased diaphragmatic excursion.
- The chest may be remarkably "quiet" in advanced stages of emphysema but is usually "noisy" in patients with chronic bronchitis.
- In advanced cases, frank cyanosis may be there from hypoxemia; a plethoric appearance associated with secondary erythrocytosis and, signs of right-sided heart failure in patients with cor-pulmonale. Mild edema may be there even without heart failure.

Chest x-ray findings:- are very variable.

- In early stages it is normal.
- Hyperinflation (e.g. depressed diaphragm, generalized radio-lucency of the lung fields) is common usually late in the disease process.
- In patients with recurrent chest infections, a variety of non-descriptive post-inflammatory abnormalities (referred to as “dirty lung”) may be noted on the chest film.

Diagnosis:

- COPD should be suspected in any patient with chronic productive cough and/or exertional dyspnea of uncertain etiology, or whose physical examination reveals evidence of prolonged forced expiration.
- Pulmonary function tests (spirometric testing) are done at specialized hospitals to determine the type of pulmonary obstruction.
- Red cell counts may reveal erythrocytosis and elevated hematochrit in chronic hypoxemic patients.
- The pattern of physiologic abnormality in each patient depends to some extent on the relative severity of intrinsic bronchial disease and emphysema. In patients with severe emphysema, resting hypoxemia is usually mild (i.e. no or less cyanosis). In patients with chronic bronchitis, severe hypoxemia may be noted relatively early.

Table II-5-1 Summary of clinical manifestations of Chronic Bronchitis and Emphysema

	Predominant emphysema	***Predominant C. bronchitis***
Age	60 +/-	50+/-
Body habitus	Thin	obese
Cough	After dyspnea	Before dyspnea
Sputum	Scanty, mucoid	Copious, purulent
Appearance	Pink, tachypneic (pink puffers)	Cyanosed, normal RR (blue bloaters)
P/E	↑AP diameter, Use of accessory muscles of respiration Silent chest, Hyperresonant Decreased cardiac dullness	+/- use of accessory muscles of respiration No hyperresonance Rhonchi (changing) Wheezing with cough
CXR	Long, narrowed tubular heart, Low diaphragm (flat diaphragm) Dark lung fields (translucent) with loss of peripheral vascular markings	Enlarged heart Large pulmonary artery Increased bronchovascular markings
Hematology	Normal Hct	Increased Hct
Blood gases	PaO_2 =65– 75mmH $PaCO_2$ = 35 – 40mmHg	PaO_2 = 40 – 60mmHg $PaCO_2$ = 50 – 60mmHg
Complications	Less bronchial infection Terminal respiratory insufficiency +/- cor-pulmonale	Frequent bronchial infection Repeated respiratory insufficiency Frequent cor-pulmonale

Course and Prognosis

In the early stage of COPD, some reversal of airway obstruction and considerable symptomatic improvement can often be obtained with therapy, but the long-term prognosis is less favorable in such patients.

Treatment: so far no curative treatment.

- Therapy is directed at relieving symptoms, controlling potentially fatal exacerbations, and slowing of the progression of the disorder.
- Avoidance of bronchial irritants, especially cessation of smoking, is of primary importance.

Thus, the treatment is outlined as follows:

1) **Treatment of infection**: COPD patients with purulent sputum should be treated with a broad spectrum antibiotic. Commonly used drugs include co-trimoxazole 980mg POBID or TTC or Ampicillin 250 - 500mg four times a day for 10 days. The course can be repeated at the first sign of recurrence of bronchial infection.
2) **Control of bronchospasm**: β-agonists like salbutamol, or one of the theophyllines can be used. Corticosteroids do not have a major role in maintenance treatment.
3) **Facilitation of drainage of bronchial secretion**: adequate hydration with oral fluids is essential to prevent drying of secretions. Inhalation of mist, postural drainage, and chest exercise may help.
4) **Hypoxemia:** this will lead to cor-pulmonale in patients with predominant c.bronchitis. Oxygen should be given in such patients with hypoxia, and in severe cases a portable oxygen therapy (16 hrs /day) for home use is recommended.
5) **Control of heart failure**: the most important measures are correction of hypoxemia, administration of diuretics and restriction of sodium intake.
6) **Exercise**: prolonged inactivity leads to exercise intolerance. Regular exercise as long as there is no severe heart disease is recommended.
7) **Depression**: The nature of the disease should be well understood by both the patient and the family. Psychological support is very important. Antidepressants may be necessary but they should be used cautiously to avoid sedation.
8) **Treatment of exacerbation**: exacerbation requires prompt treatment. If sputum becomes purulent, a course of broad-spectrum antibiotics should be given.
9) **Phlebotomy:** hematochrit is usually high because of the chronic hypoxemia (polycythemia) especially in patients with predominant chronic bronchitis. Phlebotomy

should be done when the hematocrit level is very high (above 55%) and patients are symptomatic.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Chronic obstructive pulmonary diseases, pages 1547-1553
2) Myers R. Allen , National Medical Series for independent Study (NMS) 3rd edition Medicine, Chronic obstructive pulmonary diseases , 70-74

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6. Suppurative lung diseases

6.1 Bronchiectasis

Learning Objective: At the end of this unit the student will be able to

1. *Define bronchiectasis*
2. *List the etiologies of bronchiectasis*
3. *Explain the epidemiology of bronchiectasis*
4. *Describe the pathophysiology of bronchiectasis*
5. *Identify the clinical manifestations of bronchiectasis*
6. *Describe the most commonly used tests for the diagnosis of bronchiectasis*
7. *Make a diagnosis of bronchiectasis*
8. *Give treatment for bronchiectasis at the primary care level*
9. *Design appropriate methods of prevention of bronchiectasis*

Definition: It is a pathologic, irreversible destruction and dilatation of the wall of bronchi and bronchioles, usually resulting from suppurative infection in an obstructed bronchus.

Etiology and pathogenesis:

- Small bronchi of children are susceptible to recurrent infections and obstruction by foreign body, lymph node, or impacted secretions, all of which lead to persistent infection and the development of bronchiectasis. However, bacterial pneumonia is the commonest cause of bronchiectasis. Predisposing conditions include congenital disorders (e.g. bronchial stenosis) and immunosuppressive disorders.

Clinical features

- Chronic cough productive of copious and offensive purulent sputum is the cardinal feature of bronchiectasis. The sputum typically forms three layers when collected in a glass container: the upper layer is foam (mucus), the middle one is liquid and the lower one is sediment.
- In the early stage of the disease cough and sputum production are related to cold exposure, with occasionally hemoptysis.
- In advanced disease patients have progressive dyspnea, massive hemoptysis and cough occurs at any time of the day and produces large volume of khaki colored sputum with accompanying cyanosis and clubbing.

- Complications in advanced cases include recurrent hemoptysis, cor-pulmonale, respiratory failure, amyloidosis and recurrent pneumonia.

Diagnosis

- Diagnosis is largely based on clinical features. Obtaining a history of recurrent pulmonary infections ultimately followed by chronic recurrent cough and production of copious purulent sputum may suggest a diagnosis of bronchiectasis.
- Physical examination of the chest may show only rales in early stages. Additional findings like cyanosis, clubbing and signs of right heart failure appear late.
- Pulmonary function test may be normal in early disease.
- Chest x-ray usually shows peribronchial fibrosis or it can have a honeycomb appearance. Segmental lung collapse may be observed in parts of the lung affected by bronchiectasis.
- Definitive diagnosis of bronchiectasis is made by bronchography.
- CT scanning often identifies the lesions, eliminating the need for bronchoscopy and contrast studies.

Treatment

Generally, patients should avoid smoking and exposure to dust. Living in warm & dry climatic condition is advisable. However, medical therapy is the mainstay of treatment and include

1) ***Control of respiratory infections*** :
   a. Broad spectrum antibiotics that should be given whenever signs of pulmonary infection appear and symptoms are exacerbated (Ampicillin, tetracycline or erythromycin),
   b. Immunization for influenza and *S. pneumoniae* if available
2) ***Improve drainage of secretion***: using postural drainage, liquefaction and bronchodilators.
3) ***O_2 therapy:*** may be given in patients with hypoxemia.
4) ***Surgical resection*** of the affected part is indicated when bronchiectasis is localized, and in those with recurrent massive hemoptysis that fails to respond to conservative treatment. This is effective if done early in life.

6.2 Lung abscess

Learning Objective: At the end of this unit the student will be able to

1. *Define lung abscess*
2. *List the etiologies of lung abscess*
3. *Explain the risk factors for lung abscess*
4. *Identify the clinical manifestations of lung abscess*
5. *Describe the most commonly used methods for the diagnosis of lung abscess*
6. *Make a diagnosis of lung abscess*
7. *Identify the complications of lung abscess*
8. *Give treatment for lung abscess at the primary care level*
9. *Design appropriate methods of prevention of lung abscess*

Definition: lung abscess is defined as collection of pus within a destroyed portion of the lung. It may develop following necrotizing infections of the lung (bacterial pneumonia, TB, fungi), loss of blood supply to a part of the lung causing cavitary infarction due to septic or bland embolism, obstruction to airways or cavitations of malignancy. The anaerobic abscess is the commonest and usually follows periodontal diseases (gingivitis, pyorrhea) or aspiration of oro-pharyngeal/gastric contents.

Etiology:

- Lung abscess is commonly caused by pyogenic bacteria: *S.aureus, Klebsiella*, mixed anaerobes, and *Nocardia.*
- Common risk factors include alcoholism, immunodeficiency, loss of consciousness, and periodontal diseases

Clinical features:

- In the early stage manifestations of lung abscess may resemble that of pneumonia.
- The development of features of lung abscess within 1-2 weeks after bacterial pneumonia, possible aspiration or bronchial obstruction is usually reported.
- Patients will have cough with sudden expectoration of massive purulent and foul smelling sputum, high grade fever, and sweating with occasional hemoptysis.

Diagnosis:

When patients present with the typical manifestations outlined above, the diagnosis of lung abscess may not difficult. However, it should be confirmed by chest x-ray by

demonstrating parenchymal infiltrates with cavity containing air-fluid level. Gram stain and culture of the sputum help to make etiologic diagnosis.

Complications include

- Metastatic brain abscess
- Fatal hemoptysis
- Empyema
- Secondary amyloidosis

Treatment

Medical therapy is the main stay of treatment. Admit patients to hospitals and the following modalities of therapy can be given:

1) ***Antibiotics*** – start empirical antibiotics until laboratory results are available and adjust drugs accordingly. Start both crystalline penicillin and chloramphenicol high doses IV and treatment should be given for 4 – 8 weeks.
2) ***Drainage of abscess*** – postural drainage can be effective but bronchoscopic drainage may be used when airway obstruction by foreign body or mass hinders drainage of pus by postural means. Bronchoscopes and experts who can do such procedures are available only in specialized hospitals.
3) ***Surgical treatment*** of lung abscess may be indicated in patients with
   - Persistent or massive hemoptysis
   - Empyema or bronchopleural fistula
   - Failure of medical treatment
   - Lung cancer

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Bronchiectasis, pages 1541-1542.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Bronchiectasis, 78-80.

7. *Pleurisy and Pleural Effusion*

Learning Objective: At the end of this unit the student will be able to

1. *Define pleurisy and pleural effusions*
2. *Classify pleural effusions*
3. *List the etiologies of pleural effusions*
4. *Describe the pathophysiology of pleural effusions*
5. *Identify the clinical manifestations of pleural effusions*
6. *Describe the most commonly used method of diagnosis of pleural effusions*
7. *Make a diagnosis of pleural effusions*
8. *Give treatment for pleural effusions at the primary care level*

Definition: pleural effusion is the presence of excess fluid in the pleural space. Normally 10–20 ml of fluid is spread in a thin layer between the two layers of pleurae. Pleural effusions are classified as transudates and exudates based on laboratory analysis of the fluid.

Transudative effusion: results from elevations in hydrostatic pressure or decrease in oncotic pressure. The following are some of the causes:-

- Heart failure
- Cirrhosis of the liver
- Nephrotic syndrome
- Myxoedema
- Hypoproteinemia

Exudative effusion: is due to pleural inflammation (pleurisy) with an increased permeability of the pleural surface to protein. Pleurisy commonly occurs in infections such as pneumonia, infections of the esophagus, mediastinum or sub-diaphragmatic areas, traumatic injuries, and extension of infections from adjacent organs. Initially pleurisy tends to be dry but fluid starts to collect subsequently. It is found in association with:-

- Parapneumonic effusions
- Empyema
- Pulmonary embolism
- Neoplasms
- Systemic lupus erythematosis and rheumatoid pleural effusion
- Sub-diaphragmatic abscess

- Pancreatitis
- Uremic pleural effusion
- Hemothorax
- Chylothorax (thoracic duct injury)
- Radiation and drugs.

Clinical findings and diagnosis

- Pleuritic chest pain and dyspnea are the most common symptoms, but many pleural effusions are asymptomatic and discovered on physical examination or chest x-ray.
- Underlying causes should be suspected from the history.
- Physical examination on the affected side discloses the presence of decreased chest motion, absent tactile fremitus, percussion dullness, and decreased or absent breathes sounds.

Diagnosis and laboratory findings

- The diagnosis of pleural effusion can be suspected from a properly done physical examination.
- Chest x-ray is the most precise way to confirm the physical findings. It demonstrates the presence of pleural fluid as homogenous opacity with a meniscus-sign and obliteration of the costophrenic angle. Large pleural effusions may result in complete opacification of the hemithorax and mediastinal shift to the opposite side. The best way to identify and localize a loculated pleural effusion is with ultrasonography.
- Pleural thoracenthesis (aspiration of fluid) should be performed to confirm the presence of fluid and to determine its characteristics, including color and consistency.
    - Clear yellow fluid is described as serous
    - Bloody or blood-tinged fluid as sanguineous or serosanguineous. Some of the causes include pulmonary infarction and pleural carcinomatosis
    - Translucent or opaque, thick fluid as purulent.
- Microscopic examination of the fluid is important including Gram stain and culture (if possible).
- Total and differential cell counts should be obtained.
    - The predominance of polymorphonuclear leukocytes suggests an underlying pneumonia with a parapneumonic effusion.
    - The presence of many small mature lymphocytes, particularly with few mesothelial cells, strongly suggests tuberculosis.

- It is important to determine whether pleural fluid is an exudate or a transudate; this gives a clue to the underlying cause. Exudative effusions have at least one of the following characteristics, whereas transudates have none of these:
    - Pleural fluid protein/ serum protein > 0.5
    - Plural fluid LDH/serum LDH > 0.6
    - Pleural fluid LDH more than 2/3 normal upper limit for serum
- If effusion is exudative, gross description of fluid, glucose level, amylase level, WBC and differential count, microbiologic studies, and cytology should be obtained.

Treatment:

- Therapeutic thoracenthesis should be done in massive effusion to relieve respiratory distress. Removal should be limited to 1200 to 1500 ml at a time.
- Definitive treatment of pleural effusion requires identifying the underlying condition and administration of specific therapy.
    - Tuberculous effusion is treated with a course of anti tuberculous drugs.
    - Parapneumonic effusions and other bacterial infections in the pleural space should be treated with long course of antibiotics.
    - Empyema (purulent fluid in the pleural cavity) is treated with high doses of parenteral antibiotics coupled with surgical drainage (Chest tube insertion).

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Disorders of the pleura, pages 1565-1568.

2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Diseases of the pleura, 88-91.

8. Neoplasms of the lung

Learning Objective: At the end of this unit the student will be able to

1. *Classify lung neoplasms*
2. *List the etiologies of lung neoplasms*
3. *Identify the clinical manifestations of lung neoplasms*
4. *Describe the most commonly used method of diagnosis of lung neoplasms*
5. *Make a diagnosis of lung neoplasms*
6. *Refer patients with lung neoplasms to hospitals for further investigations and treatment*

- Metastatic tumors are more common than primary tumors of the lungs; the commonest primary sites being the breasts, stomach, prostate, and ovary.
- Majority (90 – 95%) of primary lung tumors are malignant epithelial tumors collectively called bronchogenic carcinomas. The remaining are bronchial carcinoids, mesenchymal tumors (lymphomas, sarcomas, liomyomas, lipomas, fibromas, liomyosarcomas) and bronchial hemartomas, the last being benign tumors with aberrant differentiation of the bronchial tissues. The disease is common between the age ranges 65 – 75 years, and affects men more than women, with M: F ratio of 2:1.

Etiology*:* A number of factors have been found to be associated with lung cancer and include

- **Cigarette smoking** - cigarettes contain at least 55 carcinogens and the risk of lung cancer increases to 20 fold for people who smoke more than 40 cigarettes/d. Smokers have 10 times more risk of dying from lung cancer than non-smokers.
- Exposure to Radon in **underground miners** (occupational) or **indoors**
- Exposures to other carcinogens :Ni, Co, Cr, Asbestos, Polycyclic aromatic hydrocarbons, Silica , Mustard gas (world war I)

Pathologic features of bronchogenic carcinomas: originate from the bronchial epithelium and have 4 histological types

- Adenocarcinoma (including bronchoalveolar carcinoma) account for 30 - 35% of bronchogenic ca
- Squamous cell carcinoma accounts for 25 -30%
- Small cell (Oat cell) carcinoma accounts for 15 – 25%
- Large cell carcinoma accounts for 10 – 15%

- Mixed cell type (Squamous & small cell or squamous cell & adenocarcinoma) account for 5 - 10%
- Pleomorphic carcinoma (mixed carcinoma & sarcomatoid pattern) 0.5%

Differentiation between small cell and non-small cell carcinoma (Adenocarcinoma, Squamous cell ca, large cell ca) is very important because small cell carcinoma is responsive (at least initially) to chemotherapeutic treatment.

All lung neoplasms are very aggressive, invasive and widely metastasizing commonly to liver, adrenals brain and bones; they also produce bioactive hormones and other products.

Cigarette smoking is closely linked to squamous cell ca, small cell ca and large cell ca but not to adenocarcinoma

Adenocarcinoma

- More common in women than men & develop in the periphery of the lung
- Commonest lung cancer in non-smokers
- Some adenocarcinoma arise from an area of pulmonary fibrosis/scar (old infarcts, asbestosis, or on healed TB scars) which are referred to as scar cancers
- Distant organ metastases occurs in over 50% of cases, especially to the brain
- Have poor prognosis – 5 year survival is 10 -12%

Squamous cell carcinoma

- More common in males than females
- Strongly associated with cigarette smoking
- Arise centrally in the major or segmental bronchi & spread to hilar lymph nodes in 70 – 90% of cases or to distant nodes in 50 -60% of cases or to viscera
- Has poor prognosis – 5 year survival is only 5 – 8%

Small cell carcinomas

- Very aggressive and early metastasizing
- More common in males than females
- Strongly associated to cigarette smoking
- Centrally located
- Commonly associated with paraneoplastic syndromes
- Poor prognosis – 5 year survival is only 5 – 8%

Large cell carcinomas

- Anaplastic (undifferentiated) tumors, and occur in smokers

- Central or peripheral locations
- Metastasizes very rapidly and widely

Clinical features of lung carcinomas are variable.

- Some may present with local pulmonary symptoms. Others present with symptoms referable to metastasis before local pulmonary symptoms.
- About 10 - 15% of lung tumors are detected by chance (a coin shaped lesion on chest x-ray). Manifestations could be related to local obstruction, local tumor invasion, distant metastasis or ectopic hormone secretions by tumor cells (paraneoplastic syndromes).
- Local symptoms depend on the location of the tumor. When tumors are endobronchial cough, hemoptysis, stridor, wheezes, dyspnea, and nonresolving pneumonia may predominate. Pleuritic chest pain is common with peripheral tumors.

Local tumor invasion and obstruction may result in

- Recurrent laryngeal nerve palsy causing hoarseness of voice
- Phrenic nerve paralysis with diaphragm paralysis
- Esophageal obstruction causing dysphagia
- Superior vena cava obstruction presenting with edema of the face
- Pancoast syndrome is said to exist when apical lung tumors infiltrate the spinal nerves (C8 – T1) and cause shoulder pain, & cervical sympathetic nerves causing Horner's syndrome which is characterized by absence of sweating, eyelid drooping and pupillary constriction on the affected side.
- Pericardial or pleural effusions, and bronchial obstruction leading to atelectasis, pneumonia, and lung abscess

Paraneoplastic syndromes:

- Occur in 10 – 15% of bronchogenic carcinoma and the manifestations are related to ectopic hormone secretions by tumor cells**.** The manifestations could be systemic, or related to different systems.
- Systemic symptoms such as anorexia, cachexia, weight loss and fever may occur in 30% of cases.
- Another third of patients with bronchogenic carcinoma may present with endocrine manifestations like hypercalcemia or hypocalcaemia (from ectopic secretion of parathormone or calcitonin), Cushing's syndrome (from ectopic secretion of ACTH),

gyneacomastia (from ectopic secretion gonadotrophins) and inappropriate release of ADH causing Na^+ & water retention.

- Additionally patients may present with clubbing, migratory thrombophlebitis, cerebellar degeneration, neuropathies and myopathies such as Eaton-Lambert syndrome or myasthenia gravis, anemia, and thrombocytopenic purpura.

Diagnosis

Screening

- Is mandatory for men over 45 years, and those smoking more than 40 cigarettes/day
- Screened tumors were resectable in 62% of cases, and nonscreened tumors were resectable only in 20%.
- Can be done by sputum cytology (to detect malignant cells), and CXR. CXR usually demonstrates solitary pulmonary nodule and about 35% of such cases are due to bronchogenic carcinoma.

Other investigations commonly used to make the diagnosis and staging of lung tumors, most of which are available in specialized hospitals

- Lymph node biopsy from enlarged scalene or supraclavicular LN to detect metastasis
- Mediastinoscopy
- Bronchoscopy
- Thoracenthesis to collect fluid for cytology
- Pleural biopsy

Management

1. Non-small cell carcinoma
   - Surgical excision is curative for patient with ipsilateral lymph node involvement but without local/distant spread or contralateral lymph node involvement.
     - Intrathoracic disease - radiotherapy is palliative
     - Pancoast syndrome – radiotherapy/chemotherapy
     - Extrathoracic disease – analgesics, radiotherapy, dexamethasone, obliteration of the pleural cavity
2. Small cell carcinoma
   - By the time of diagnosis 95% of these tumors have metastasized
   - Responsive for chemotherapy +/- radiotherapy

3. Bronchial adenomas, carcinoids need surgical resection

Prevention – Cessation of smoking

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Neoplasms of the lung, pages 506-515.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Carcinoma of the lung, 169-172.

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CHAPTER THREE
DISEASES OF THE CARDIOVASCULAR SYSTEM

Introduction

The epidemic of cardiovascular diseases (CVDs) is accelerating globally over all regions and social classes. This is reflected in the high burden as well as the estimated escalation of those burdens over the next two decades. Most current global burden of CVD as well as all of the expected future augmentation of this burden is attributable to the change in the life style of people. Even in the setting of a 'double burden' of disease which is experienced by the developing countries, CVD contributes to a large proportion of morbidity and mortality.

A major study by WHO and Harvard School of Public Health published in 1996, predicted massive rise of non-communicable diseases (NCDs), most of this rise taking place in the developing world. Already, according to the author of this report, adults under the age of 70 in Africa face a higher probability of death from NCD than their counterparts in the West. The number of people living with a disability is also set to increase.

A number of reasons underlie the expected rise in CVD in the developing world:

1. An overall increase in the population.
2. Improved life expectancy is leading to more person living to the middle age and beyond , which increase the risk of CVD
3. Lifestyle transition:-increase urbanization, industrialization, globalization and change in nutritional habit.
4. Past or current nutrition deprivation in utero and early childhood may affect cardiovascular health trend. Lack of weight gain in the first year of life and low birth weight in spite of maternal weight gain have been linked to coronary disease in adult life.

The causes of cardiovascular diseases in developing countries include:-

- Chronic rheumatic heart disease
- Hypertensive heart disease
- Cardiomyopathies
- Congenital heart disease.
- Ischemic heart disease:

There are indicators of increasing prevalence of ischemic heart diseases due to the existence of risk factors in some segment of the population: hypertension, smoking, diabetes, hypercholesterolemia, and obesity.

There are very few studies about CVD in Ethiopia. The prevalence of rheumatic heart disease is 6/1000 in school children. Analysis of admitted cases, to medical ICU of Tikur Anbessa Hospital from 1988 to 1997 (in Addis Ababa, Ethiopia) has showed that acute myocardial infraction (AMI) was the third cause of ICU admission, and AMI annual admission increased consistently. Moreover, from one year (1998 - 1999) autopsy study done in Minilik II Hospital to investigate the cause of sudden death in Addis Ababa, 70% (44/63) deaths were found to be due to coronary artery disease.

The implication of a CVD epidemic is devastating to developing countries in general and to Ethiopia in particular, as there are few community-based programs and government policies to limit the spread of deleterious health behaviors. Therefore, there is a need to carry out appropriate preventive strategies to tackle the problem.

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1. Rheumatic Fever

Learning objectives: at the end of this lesson the student will be able to :

1. *Define rheumatic fever*
2. *Understand the etiologic agents of rheumatic fever*
3. *Understand the Epidemiology of rheumatic fever*
4. *Describe the pathogenesis of rheumatic fever*
5. *Identify the clinical manifestation of rheumatic fever*
6. *Understand the diagnostic approach of rheumatic fever*
7. *Manage patients having rheumatic fever*
8. *Design strategies for prevention of rheumatic fever*

Background: Rheumatic fever causes chronic progressive damage to the heart and its valves .The association between sore throat and rheumatic fever was not made until 1880. The dramatic decline in the incidence of rheumatic fever in the developed world is thought to be largely owing to antibiotic treatment of streptococcal infection, though it stated to decline before the era of antibiotic, probably due improvement of socioeconomic status.

Epidemiology

- Even though the overall incidence of RF and RHD in developed countries has sharply declined, rheumatic fever is the commonest cause of heart disease in the developing countries. In those countries, more than 50% of heart disease is accounted for rheumatic heart disease (RHD). Even in developing countries, the prevalence of RF and RHD varies between rural and urban areas.
- The Prevalence of RF ranges from 3 to 12/1000 population in the developing country with the peak age of 5-15 years.
- In adult the risk developing of RF is about 3% following group A Streptococcal (GAS) Pharyngitis with a recurrence rate of 1/6.
- The high attack rate of group A Streptococcal pharyngitis in families, institutions and military recruits is the result of contact among susceptible persons living closely enough to ensure droplet transmission.
- Risk factors for RF include low socioeconomic status with associated over crowded living condition. However, RF is not associated with streptococcal skin infection (pyoderma).

Pathophysiology

- Acute rheumatic fever is a sequel of a previous group A streptococcal infection, usually of the upper respiratory tract. One beta-streptococcal serotype (e.g., M types 3, 5, 18, 19, 24) is linked directly to acute rheumatic fever. Rheumatogenicity of GAS is important factor as not all GAS pharyngitis is associated with development of rheumatic fever.
- Rheumatic fever follows Lancefield β hemolytic streptococcus pharyngitis within the interval of 2-3 weeks.

The mechanism is elusive, but the followings are proposed ones:

- Dysfunction of the immune Response
- Antigenic Mimicry
    - Similarity between the carbohydrate moiety if GAS and glycoprotein of heart valve
    - Molecular similarity between some Streptococcal antigens and sarcolema or other moiety of human myocardial cells.
- Several host related factors have been identified to have operated in relation to specific genetic function and difference in the immune response of individuals.
- The disease involves the heart, joints, central nervous system (CNS), skin, and subcutaneous tissues. It is characterized by an exudative and proliferative inflammatory lesion of the connective tissue, especially that of the heart, joints, blood vessels, and subcutaneous tissue.

Clinical Manifestation

Acute rheumatic fever is associated with 2 distinct patterns of presentation.

- The first pattern of presentation is sudden onset. It typically begins as polyarthritis 2-6 weeks after streptococcal pharyngitis, and it is usually characterized by fever and toxicity.
- The second pattern is insidious or subclinical and the initial abnormality is mild carditis.
- Age at onset influences the order of complications. Younger children tend to develop carditis first, while older patients tend to develop arthritis first.

Diagnosis:

Diagnosis of acute rheumatic fever requires a high index of suspicion.

Jones criteria developed by the American Heart Association is used to make the diagnosis.

Table III -1 -1 Jones criteria for the diagnosis of acute rheumatic fever.

Major Criteria	***Minor Criteria***
Carditis Migratory ply arthritis Sydenham's Chorea Subcutaneous nodules Erythema marginatum	Clinical Fever Arthralgia Laboratory Elevated acute phase reactants : ESR, CRP Prolonged PR interval
Plus Supportive evidence of recent Group A streptococcal infection (e.g. positive throat culture or rapid antigen detection test ; and/or elevated or increasing streptococcal antibody test : ASO titer , Anti DNAase , Anti NADase etc)	

JAMA: 268, 2069, 1992.

In addition to evidence of a previous streptococcal infection, the diagnosis of acute rheumatic fever requires 2 major Jones criteria or 1 major plus 2 minor Jones criteria.

1) ***Carditis,*** (pancarditis here), occurs in as many as 40- 60% of patients and may manifest as:
   a) New murmur
   b) Cardiomegaly
   c) Congestive heart failure
   d) Pericarditis with or without a pericardial rub and resolve without squeal of constriction.
   e) Valvular disease: mitral and aortic valves are commonly affected. Healing of rheumatic valvulitis will lead into fibrous thickening and adhesion, resulting in progressive valvular damage. But, about 80% of mild valvulitis would resolve. There is a risk of developing endocarditis on a damaged valve.
2) ***Migratory polyarthritis*** occurs in 75% of cases and involves many joints at a time. The larger joints are mainly affected.
3) ***Subcutaneous nodules***: occur in 10% of patients and are edematous fragmented collagen fibers. They are firm painless nodules on the extensor surfaces of wrists, elbows, and knees.

4) ***Erythema marginatum*** occurs in about 5% of cases. The rash is serpiginous and long lasting.

5) ***Sydenham's chorea*** (i.e., St Vitus' dance) is a characteristic movement disorder that occurs in 5-10% of cases. Sydenham's chorea consists of rapid purposeless movements of the face and upper extremities. Onset may be delayed for several months to years and may cease when the patient is asleep.

Laboratory Studies:

- No specific confirmatory laboratory tests exist. However, several laboratory findings indicate continuing rheumatic inflammation. Some are part of the Jones minor criteria.
- ***Supportive evidences***
    - Streptococcal antibody tests disclose preceding streptococcal infection
        - ASO titer: positive in 80% of cases
        - Anti DNAase β & Anti hyaluronidase is positive in 95 % of cases
    - Isolate group A streptococci via throat culture which has 20-40% yield.
- ***Laboratory minor criteria***
    - Acute phase reactants (e.g. raised ESR and C-reactive protein [CRP])
    - Leukocytosis may be seen.
    - Anemia usually is caused by suppression of erythropoiesis.
    - ECG: PR interval prolongation is seen in 25% of all cases but is neither specific to nor diagnostic.

Treatment

Medical therapy involves the following 5 areas:

1. ***Treat group A streptococcal infection*** regardless of organism detection.

All patients with acute rheumatic fever should be given appropriate antibiotic.

- Ampicillin 500 mg PO QID or Amoxicillin 500 mg PO TID for 10 days or
- Benzathin penicillin 1.2 million IU IM single dose or
- Erythromycin 500 mg PO QID for 10 days (for penicillin allergic patient)

2. ***Therapy for manifestation of acute rheumatic fever***

Arthritis:

- ASA is given at dose 2 gm four times per day for 4-6 weeks, no indication for steroids.

Carditis

Severe Carditis with congestive heart failure should be treated with

- Prednisolone 60 to 80 mg /day, to be tapered as patient improves
- Start ASA during tapering phase to be given for 4-6weeks
- But both have no influence on the future development of valvular heart disease (VHD).

Congestive heart failure: Treats by conventional therapy such as digoxin and diuretics.

Sydenham's chorea: In majority of the cases it is self-limiting. But in symptomatic patients benzodiazepines (diazepam) or phenothiazines (haloperidol) may be helpful in controlling symptoms.

3. Administer secondary prophylaxis: is indicated for all patients with rheumatic fever.

Taking benzathin penicillin is the first choice for better compliance and longer prevention.

- Benzathin penicillin 1.2 million IU IM every 4 weeks , but if the there is high risk of recurrence, it can be given every 3weeks

Alternative antibiotics

- Oral penicillin V (250mg twice/day)
- Oral sulfadiazine (1g/day)

N.B. In a patient with an established RHD, it is advisable to get the prophylaxis lifelong.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Rheumatic fever , pages 1977-1978

2. Congestive Heart Failure

Learning objectives: at the end of this lesson the student will be able to **:**

1. *Define congestive heart failure.*
2. *List the etiologic agents of congestive heart failure.*
3. *Understand the Epidemiology of congestive heart failure.*
4. *Describe the pathophysiology of congestive heart failure.*
5. *Identify the clinical manifestation of congestive heart failure.*
6. *Understand the diagnostic approach of congestive heart failure.*
7. *Manage patients with congestive heart failure.*
8. *D*esign strategies for prevention of *congestive heart failure*.

Definition:

- Heart failure is a clinical syndrome characterized by inadequate systemic perfusion to meet the body's metabolic demands as a result of abnormalities of cardiac structure or function.
- This may be further subdivided into either systolic or diastolic heart failure.
    - Systolic heart failure: there is reduced cardiac contractility
    - Diastolic heart failure there is impaired cardiac relaxation and abnormal ventricular filling.
- The body, sensing inadequate organ perfusion, activates multiple systemic neurohormonal pathways which compensate initially by redistributing blood flow to vital organs but later exacerbate the patient's symptoms and lead to clinical deterioration.

Etiology:

The most common cause of heart failure is left ventricular systolic dysfunction (about 60% to 70% of patients). The following are some of the underlying causes of heart failure .

1) *Decreased contractile function*
    a. Valvular heart disease
    b. Coronary Heart Disease : Myocardial ischemia
    c. Myocardial Disease : Cadiomyopathy , Myocarditis
2) *Increased after load*
    a. Acute systemic hypertension
3) *Abnormalities in preload*

a. Excessive preload
b. Reduced preload

4) Reduced compliance states: Constrictive pericarditis , Restrictive cardiomyopathy

Precipitating factors for heart failure:

- These are relatively acute disturbances that place an additional load on a myocardium that is chronically and excessively burdened.
- In compensated state patients are asymptomatic; however as patients have little additional reserve, they become symptomatic in the presence of these precipitating factors.
- Knowing the precipitating factors is important because most of the time they are treatable and the cardiac function improves when these precipitating factors are treated or avoided.

The most important precipitating factors may be represented with the mnemonic, ***HEART FAILES***

H- Hypertension (systemic)
E- Endocarditis (infections)
A- Anemia
R- Rheumatic fever and myocarditis
T- Thyrotoxicosis and pregnancy
F- Fever (infections)
A- Arrhythmia
I- infarction (myocardial)
L- Lung infection
E- Embolism (pulmonary)
S- Stress (emotional, physical, environment, dietary, fluid excess)

Pathophysiology

- In left ventricular systolic dysfunction, regardless of the etiology, cardiac output is low and pulmonary pressures are high, leading to pulmonary congestion. As a result, a series of adaptive mechanisms are activated. Initially, as a direct result of inadequate cardiac output and systemic perfusion, the body activates several neurohormonal pathways in order to increase circulating blood volume.
- With continuous neurohormonal stimulation, the left ventricle undergoes remodeling with left ventricular dilatation and hypertrophy, such that stroke volume is increased without

an actual increase in ejection fraction. This is achieved by myocyte hypertrophy and elongation. However, left ventricular chamber dilatation causes increased wall tension, worsens subendocardial myocardial perfusion, and may provoke ischemia in patients with coronary atherosclerosis. Furthermore, left ventricular chamber dilatation may cause separation of the mitral leaflets and mitral regurgitation with worsening of pulmonary congestion. Enhanced neurohormonal stimulation of the myocardium also causes apoptosis, or programmed cell death, leading to worsening of ventricular contractility.

Clinical Manifestations

- Progressive dyspnea which initially occurs with exertion and later occurs at rest. Dyspnea on exertion has been found to be the most sensitive complaint, yet the specificity for dyspnea is less than 60%.
- Orthopnea and paroxysmal nocturnal dyspnea (PND) are more specific symptoms; however, sensitivity for orthopnea and PND is only 20-30%.
- Cough productive of pink, frothy sputum is highly suggestive of CHF. Wheezing may also occur.
- Peripheral edema and ascites
- Nonspecific complaints include the following: easy fatigability , light headedness , malaise anxiety abdominal pain , nausea etc
- ***Past medical history*** may include the following: rheumatic fever , alcohol use, hypertension , angina , previous history of myocardial infarction and familial history of heart disease

Physical findings:

- Tachycardia and Tachypnea and signs of respiratory distress including use of accessory muscles of respiration
- Jugular venous distention (JVD) frequently is present and engorged neck veins
- Pulsus alternans (alternating weak and strong pulse indicative of depressed left ventricle [LV] function
- Wheezing or rales may be heard on lung auscultation and there may be bilateral basal dullness.
- Apical impulse frequently is displaced laterally
- Cardiac auscultation may reveal aortic or mitral valvular abnormalities, S_3 or S_4.

- Skin may be diaphoretic or cold, gray, and cyanotic
- Lower extremity edema also may be noted, especially in the subacute process.

New York Heart Association Heart Failure Classification scheme is used to assess the severity of a patient's functional limitations and correlates fairly well with cardiovascular prognosis.

Table III -2-1: New York Heart Association Heart Failure Symptom Classification System

Grade	***Symptoms***
I	No symptom limitation with ordinary physical activity
II	Ordinary physical activity somewhat limited by dyspnea (i.e., long distance walking, climbing 2 flights of stairs)
III	Exercise limited by dyspnea at mild workloads (i.e., short distance walking, climbing one flight of stairs)
IV	Dyspnea at rest or with very little exertion

Diagnostic Workup

- ***Chest x-ray***: the main findings are cardiomegally, pulmonary edema, and pleural effusion.
- ***Echocardiography***: may help identify valvular abnormalities, ventricular dysfunction, cardiac temponade, pericardial constriction, and pulmonary embolus.
- ***Electrocardiogram (ECG)***: is a nonspecific tool but may be useful in diagnosing concomitant cardiac ischemia, prior myocardial infarction (MI), cardiac dysrhythmias, chronic hypertension, and other causes of left ventricular hypertrophy.
- **Other laboratory tests :** Hemoglobin, Urinalysis, BUN, Creatinine

Management of Heart Failure

Principles of management

1. *Identify and treat the precipitating factors*
2. *Control the congestive state*
3. *Improve myocardial performance*

4. *Prevention of deterioration of myocardial function (slowing progression of heart failure)*
5. *Treat the underlying cause*

A. General measures :

- ***Dietary sodium restriction*** should be implemented in all patients with congestive heart failure to < 3 g/d.
- ***Activity and life style modification*** :
  - Meals should be small in quantity but more frequent.
  - Reduce anxiety and emotional stress
  - Avoid excess physical exertion (NB exercise may be advised within the limit of the patient's cardiac function)
  - Weight loss in encouraged in obese patients.
  - Cessation of smoking
  - Avoid other CVD risk factors

B. *Control of the Congestive state*

Diuretics: are useful in relieving congestion and reduce or prevent edema.

Most patients with heart failure have some degree of symptomatic congestion and benefit from diuretic therapy.

Usually a loop diuretic is required, with the addition of a Thiazide diuretic in patients refractory to the loop diuretic alone.

1. ***Furosomide***: Initial dose 20-40 mg PO 1-2 X daily or 20 mg IV
   Maximum dose 400 mg PO/day or 80 mg IV /day
2. ***Hydrochlorothiazide***: Initial dose 25 mg PO/day
   Maximum dose 100 mg PO/day

- N.B . Loop and thiazide diuretics are useful for symptomatic relief; however they have not been shown to improve survival.

- Side effects : Azotemia, hypokalemia, metabolic alkalosis and elevation of neurohormones

3. ***Spirinolactone***: is an aldosterone inhibitor, reduces mortality in patients with advanced heart failure. This drug should be reserved for patients with moderately severe or severe heart failure (class IV symptoms)

   Initial dose: 25 mg PO/day or every other day

   Maximum dose: 50 mg PO BID or higher

Side effects:

- ***Hyperkalemia*** is common so monitoring K^+ the serum potassium level is essential. As a result, this drug should not be used in patients with a creatinine above 2.5 mg/dl.
- ***Gynecomastia*** in men is the other side effect of this drug.

C. Enhancement of Myocardial contractility :

1) Digoxin: is a drug which has :

- ***Inotropic effect*** and acts by inhibiting the Na^+-K^+ ATPase and increase intracellular calcium. This increases myocardial contractility.
- ***Neurohormonal modulation*** of centrally mediated parasympathomimetic and sympatholytic activity. By doing so it blocks the AV node and delays AV conduction.
    - Initial dose : 0.125 mg PO/day
    - Maximum dose : 0.25 mg PO/day

- The use of digoxin can improve symptoms, reduce the duration and the need for hospitalization in patients with heart failure,, but has no effect on long term survival.
- Digoxin is renally excreted and so dose adjustment is necessary in renal failure.
- A low dose of the drug (0.125 mg daily) should be prescribed, especially in women.
- Digoxin use is recommended for patients with left ventricular systolic dysfunction, particularly if they have atrial fibrillation.
- It is relatively contraindicated in some cardiac disease
    - Cardiac outflow obstruction in MS (in the absence of atrial fibrillation)
    - Corpulmonale
- Because of it narrow window of safety, digoxin is associated with different Side effects including:
    - GI : anorexia , nausea, vomiting , weight loss
    - Neuralgia, delirium
    - Yellow vision
    - Gynecomastia
    - Arrhythmias of different types

- Electrolyte on toxicity is suspected, digoxin should be withheld, and has observe for some days before reinitiate with a lower dose. One should also give KCl, as hypokalemia is increase digoxin toxicity.

2) ***Vasodilators:*** may be useful in patients with severe acute heart failure who demonstrate systemic vasoconstriction despite ACE inhibitor therapy. Through vasodilatation they reduce the peripheral resistance and after load and improve cardiac performance.

Hydralazine: Initial dose: 25 mg PO TID

Maximum dose: 150 mg PO QID.

Isosorbide dinitrate: Initial dose 10 mg PO TID

Maximum dose: 80 mg PO TID

- Hydralazine and nitrates in combination are effective afterload reducing agents used in ACE-intolerant patients.

D. Prevention of deterioration of Myocardial function :

- The following drugs prevent deterioration in myocardial function by inhibiting the neurohumeral mechanism which causes cardiac remodelling and progression of heart failure.

1) Angiotensin Converting Enzyme (ACE) Inhibitors

Afterload reduction and neurohormonal modulation with ACE inhibitors (e.g. Captopril, Enalapril, etc) have been shown to improve mortality, symptoms, and hospitalizations. The dose of ACE inhibitors should be titrated to the maximum that can be tolerated symptomatically or the target dose. .

Initial dose: Captopril 6.25 mg PO/day or every other day

Enalapril 2.5 mg PO BID

Maximum dose: Captopril 50-100 mg PO QID

Enalapril 10- 20 mg PO BID

Side effects of ACE inhibitors

- Angioedema
- Acute renal failure I patients with bilateral renal artery stenosis. It is contraindicated in a patient with creatinine >3mg/dl
- Cough

Contraindications:

- Angioedema or anuric renal failure
- Pregnancy
- Hypotension

- Creatinine > 265 mol/L (3mg/dl)

N.B The first two side effects are serious and necessitate immediate cessation of the drug.

2) **Angiotensin-II Receptor blocker**

These drugs are useful in patients who cannot tolerate ACE inhibitors due to different side effects like cough angioedema and lukopenia.

Lasortan: Dose: - 25-50 mg once 0r twice daily

3) **Beta Adrenorecepter blockers**

Administration of these drugs with gradually increasing dose has been reported to improve symptoms of heart failure, the need for hospitalization and reduce mortality. They are indicated to moderately severe heart failure.

They are not indicated in unstable heart failure , hopotensive states , severe fluid overload , sinus bradycardia , AV block and asthma.

Metoprololol: *Initial dose 6.25 mg PO BID*

Maximum dose: 75 mg PO BID

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Heart failure, pages 1367-1377.

2. Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Congestive Heart failure,1-6.

3. Valvular Heart Diseases (VHD)

Learning objectives: at the end of this lesson the student will be able to :

1. *Define valvular heart diseases.*
2. *List the etiologies of valvular heart diseases.*
3. *Understand the Epidemiology of valvular heart diseases.*
4. *Describe the pathogenesis of valvular heart diseases.*
5. *Identify the clinical manifestation of different valvular heart diseases.*
6. *Understand the diagnostic approach of valvular heart diseases.*
7. *Understand the management of patients having valvular heart diseases.*

Introduction

- Valvular heart disease from chronic rheumatic fever is still the commonest cardiac disease in the developing world, occurring at the younger age.
- It causes significant morbidity and mortality due to lack of appropriate preventive and therapeutic intervention.
- It accounts for 42 % of cardiac patients attending hospitals in Ethiopia.
- Generally, patients with stenotic valvular lesions can be monitored clinically until symptoms appear. In contrast, patients with regurgitate valvular lesions require careful echocardiographic monitoring for left ventricular function and may require surgery even if no symptoms are present.
- Aside from antibiotic prophylaxis, very little medical therapy is available for patients with valvular heart disease; surgery is the treatment for most symptomatic lesions or for lesions causing left ventricular dysfunction even in the absence of symptoms. However surgical management is unavailable for most patients who are suffering from valvular heart diseases in Ethiopia.

Aortic Stenosis (AS)

Aortic stenosis could be caused by

- Rheumatic carditis
- Congenital stenosis of aortic valve or
- Senile/calcific aortic stenosis which is idiopathic results in calcification and degeneration of the aortic leaflets.

- Persons born with a bicuspid aortic valve are predisposed to develop aortic stenosis.

Clinical features

Initially there is an extended latent period during which the patient is asymptomatic. This is followed by the classic symptoms of AS:

- Angina
- Exertional syncope and
- Dyspnea

Physical Examination

- The most common physical sign of aortic stenosis is a systolic ejection murmur at left at the 2nd intercostals space that radiates to the neck. In mild aortic stenosis, the murmur peaks early in systole, but as the severity of stenosis increases, the murmur peaks progressively later in systole and may become softer as cardiac output decreases
- As the stenosis worsens, the aortic component of the second heart sound may become diminished.
- The timing and amplitude of the carotid pulse correlate with the severity of aortic stenosis. Later in the disease, the carotid upstrokes become diminished and delayed (parvus et tardus)

Echocardiography

- Echocardiography with Doppler provides an accurate assessment of aortic valve area and transvalvular gradient and also can be used to estimate left ventricular hypertrophy and ejection fraction.

Chest X-ray: may demonstrate valve calcification.

Management

Medical Therapy:

- Is not effective and treatments with digitalis or cautiously administered diuretics may only reduce symptoms.
- Patients with severe aortic stenosis should limit vigorous physical activity.
- Patients with aortic stenosis are at moderate risk for development of endocarditis and should receive endocarditis prophylaxis before selected procedures.

Surgical Therapy

- Aortic valve replacement is the only effective treatment that will relieve this mechanical obstruction.

Prognosis:

- The survival of patients with aortic stenosis is nearly normal until the onset of symptoms, when survival rates decrease sharply.
- Although the rate of progression of aortic stenosis is variable and difficult to predict approximately 75 percent of patients with aortic stenosis will be dead three years after the onset of symptoms if the aortic valve is not replaced.

Aortic Regurgitation (AR)

Aortic regurgitation results from disease affecting the aortic root or aortic leaflets, preventing their normal closure.

Common causes of aortic regurgitation include:

- Endocarditis
- Rheumatic fever
- Collagen vascular diseases
- Aortic dissection
- Syphilis
- Bicuspid aortic valves are also prone to regurgitation.

♦ In chronic aortic regurgitation, the stroke volume is increased, which in turn causes systolic hypertension, high pulse pressure and increased afterload. The afterload in aortic regurgitation may be as high as that occurring in aortic stenosis.

♦ Patients may be asymptomatic until severe left ventricular dysfunction has developed. The initial signs of aortic regurgitation are subtle and may include decreased functional capacity or fatigue. As the disease progresses, the typical presentation is that of left-sided heart failure: orthopnea, dyspnea and fatigue.

♦ Systolic dysfunction is initially reversible, with full recovery of left ventricular size and function after aortic valve replacement. Over time, however, progressive chamber enlargement with decreased contractility make recovery of left ventricular function and improved survival impossible, even with surgery.

Physical Examination:

- A diastolic blowing murmur heard along the left sternal border is characteristic of aortic regurgitation. A diastolic rumble may also be heard over the apex.
- The peripheral signs of hyperdynamic circulation indicate severe disease. Some of these include:
    - Wide pulse pressure
    - Collapsing pulse (water hammer pulse)
    - Quincke's pulse (alternating blanching and erythema of the nailbed with gentle pressure applied)
    - De musset's sign (head bobbing)
    - Pistol shot over the femoral artery

Echocardiography

- Echocardiography with Doppler ultrasonography provides information about aortic valve morphology and aortic root size, and a semiquantitative estimate of the severity of aortic regurgitation .It provides valuable information about left ventricular size and function.

Management

Medical Treatment

- Diuretics
- Digoxine: may be indicated in patients with severe regurgitation and dilated left ventricle without frank LV failure.
- Salt restriction
- Vasodilators: afterload reduction with vasodilators has been shown to improve left ventricular performance and reduce aortic regurgitation. ACE inhibitors are the preferred vasodilators. Therapy with long acting nifedipine in particular has been shown to delay the need for surgery by two to three years.
- Endocarditis prophylaxis is essential for all patients with AR as their infection tolerance is poor.

Surgical management: aortic valve replacement is the definitive treatment for patients with AR. There are two important points to consider in deciding the timing of surgery.

1. Patients with chronic AR usually don’t become symptomatic until after the development of myocardial dysfunction

2. When delayed too long, surgical treatment often does not restore normal LV function.

- There for appropriate timing is necessary for surgical intervention.

Aortic regurgitation should be corrected if the symptoms are more than mild. Compelling evidence supports surgical correction before the onset of permanent left ventricular damage, even in asymptomatic patients.

Mitral Stenosis (MS)

- Mitral stenosis is sequelae of rheumatic heart disease primarily affecting women.
- Mitral stenosis has a progressive, lifelong course that is slow and stable in the early years, with rapid acceleration later in life.
- It is very common in the developing countries manifesting below the age of 20 whereas there is generally a latent period of 20 to 40 years between the occurrence of rheumatic fever and of mitral stenosis in developed countries.
- Elevated left atrial pressure eventually causes pulmonary vasoconstriction, pulmonary hypertension and compromise of right ventricular function.
- Many patients remain asymptomatic until atrial fibrillation develops or until pregnancy occurs, when there is increased demand on the heart.
- Symptoms are generally those of left-sided heart failure: dyspnea on exertion, orthopnea and paroxysmal nocturnal dyspnea. Patients may also present with hemoptysis, signs of right-sided heart failure, and embolic phenomena like stroke.

Physical Examination

- An apical rumbling, mid-diastolic murmur is characteristic and will immediately follow an opening snap, if present. The rumble is loudest in early diastole but, in patients with mild mitral stenosis or mitral stenosis with low cardiac output, the murmur may be difficult to hear. It can be accentuated by placing the patient in the left lateral decubitus position and using the bell of the stethoscope. Brief exercise (such as walking in the hallway) may also accentuate the murmur.
- A loud first heart (S1) sound is common.
- A right ventricular lift, elevated neck veins, ascites and edema are later signs of right ventricular overload with pulmonary hypertension.

Complication of MS

- Atrial fibrillation
- Thromboembolism
- Right sided hear failure

Echocardiography

- Echocardiography is the study of choice for diagnosing and assessing the severity of mitral stenosis.

Chest X-ray may show left atrial enlargement and sign of pulmonary congestions.

Management

In asymptomatic patients

- Annual evaluation (history and physical examination, as well as a chest x-ray and ECG).
- Endocarditis prophylaxis
- Secondary prophylaxis for reumatic fever

In patients with symptoms:

Medical treatment

- Diuretics may be helpful in reducing left atrial pressure and decreasing symptoms.
- Digoxin: is indicated for patients with atrial fibrillation to control the heart rate, since tachycardia will further decrease left ventricular filling, reduce cardiac output and increase left atrial pressure, leading to more symptoms.
- Anticoagulants such as Warferin may be indicated in patients with Left atrium and atrial fibrillation.

Surgical management: improves survival and reduce symptoms.

- Open commissurotomy or
- Mitral valve reconstruction or
- Mitral valve replacement.

Mitral Regurgitation (MR)

Causes of chronic mitral regurgitation include:

- Rheumatic fever
- Infective endocarditis
- Degenerative valvular disease (mitral valve prolapsed).
- Myocardial infarction affecting papillary muscles.

Pathophysiology:

Chronic mitral regurgitation is a state of volume overload leading to the development of left ventricular hypertrophy. The left atrium also enlarges to accommodate the regurgitate volume. This compensated phase of mitral regurgitation varies in duration but may last many years. The prolonged state of volume overload may eventually lead to decompensate mitral regurgitation. This phase is characterized by impaired left ventricular function, decreased ejection fraction and pulmonary congestion.

The common symptoms are:

- Fatigue, Exertional dyspnea and orthopnea are the most common complaints.
- Right sided heart failure with painful hepatic congestion, peripheral edema may occur in patients with MR who have associated pulmonary hypertension.

Physical Examination

- A soft first heart sound (S1 is generally absent) and a widely split second heart sound may be present.
- An S_3 gallop indicates severe disease but does not necessarily indicate heart failure
- There may be displacement of the left ventricular impulse
- A holosystolic murmur that may radiate to the axilla, the upper sternal borders or the subscapular region is apparent on physical examination.

Echocardiography

- Echocardiography can be used to determine the etiology and morphology of mitral regurgitation, which are important in determining suitability for mitral valve repair.

Chest X-ray: Enlargement of LA and LV , Pulmonary venous congestion and interstitial edema and Kerley-B lines .

Management

Medical Treatment:

- Diuretics
- Digoxin: may be indicated in patients with severe regurgitation and dilated left ventricle without frank LV failure.
- Salt restriction
- Vasodilators: afterload reduction with vasodilators has been shown to improve left ventricular performance.. ACE inhibitors are the preferred vasodilators.
- Treatment of atrial fibrillation if it occurs
- Endocarditis prophylaxis is important essential..

Surgical Treatment: Mitral valve replacement is the definitive treatment.

- In patients with chronic mitral regurgitation, left ventricular damage can occur while the patient remains asymptomatic. Therefore, surgery is indicated if left ventricular dysfunction has begun to develop, even in the absence of symptoms.
- Patents with MR who are asymptomatic and whose LV function are normal are not considered to be candidates for surgical treatment.

Tricuspid Regurgitation (TR)

- TR is functional and secondary to marked dilatation of tricuspid annulus The most common cause of TR is pulmonary hypertension as result of left sided cardiac failure or pulmonary parenchymal/vascular disease.
- Less common causes include rheumatic HD, right sides myocardial infarction , and endocarditis in IV drug abusers.

Clinical features

- In patients with pulmonary HTN symptoms of pulmonary congestion diminish, but the symptoms of right sided heart failure are intensified such as peripheral edema and ascites.
- Patients will have prominent jaguar venous distention
- Holosystolic murmur at the left lower sternal border.
- Pulsatile liver and
- More prominent ascites than edema is a common finding.

Echocardiography

- It is a very useful study, and it differentiates primary from secondary TR.

Management:

- Treatment of the underlying cause of heart failure usually reduces the severity of functional TR.
- Surgical treatment as indicated for primary TR.

Mitral Valve Prolapse

- Mitral valve prolapse occurs when varying portions of one or both leaflets of the mitral valve extend or protrude abnormally above the mitral annulus into the left atrium.
- MVP has different causes
    - Redundant or excessive mitral valve tissue
    - Congenital diseases such as Marfan's syndrome , osteogenesis imperfecta.

- Although the prevalence of mitral valve prolapse was once thought to be as high as 15 percent in the general population, more recent studies using new echocardiographic criteria for diagnosis have suggested a prevalence of approximately 2.4 percent.

Clinical futures

- MVP is more common in females and more common in the age group of 14-30.
- The clinical course is often benign
- Most patients are asymptomatic and may remain so for their entire lives.
- Some patients may manifest with features of Mitral regurgitation
- Arrhythmias like premature ventricular contractions and ventricular tacycardias may occur as complications.
- The mid-systolic click, often accompanied by a late systolic murmur, is the auscultatory hallmark of mitral valve prolapse.

Management

- Asymptomatic patients may need only reassurance
- Symptomatic patients with thickening of mitral valve
    - Endocarditis prophylaxis is
    - B- blockers sometimes may relive chest pain
- Sever symptoms from secondary MR: surgical treatment may be needed (mitral valve repair and or rarely replacement.)

Summery

- Even though the definitive management for most valvular heart diseases is surgical intervention to correct the underlying valvular abnormality , in the current Ethiopian setup, surgical interventions are not affordable and not available in the country. Hence the general management is treatment of the congestive heart failure state.
- The onset of symptoms in the developing world occurs at an earlier age because of repeated attack of recurrent rheumatic fever. Increased left atrial pressure and decreased cardiac output produce the symptom. Therefore both primary and secondary preventions are paramount importance to reduce the morbidity and mortality
- Great progress has been made in improving rates of morbidity and mortality in patients with valvular heart disease. Successful management of patients with valvular heart disease requires an evidence-based approach to echocardiography and to surgical intervention.

- Echocardiography should assess not only the valvular lesion but also the compensatory changes of the heart in response to the lesion.
- Timing of surgical intervention often correlates with outcome.
- Most patients with acquired valvular heart disease are at risk for developing endocarditis and should receive prophylactic antibiotics.

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Valvular Heart Diseases, pages 1390-1402.

2. Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Valvular Heart Diseases, 29-37.

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4. Infective Endocarditis

Learning objectives: at the end of this lesson the student will be able to**:**

1) *Define valvular heart Infective endocarditis.*
2) *List the etiologic agents of Infective endocarditis.*
3) *Describe the different types of Infective endocarditis.*
4) *Understand the Epidemiology of Infective endocarditis.*
5) *Describe the pathogenesis of Infective endocarditis.*
6) *Identify the clinical manifestation of Infective endocarditis.*
7) *Understand the diagnostic approach of Infective endocarditis.*
8) *Understand the management of patients having Infective endocarditis*.

Definition: Infective endocarditis (IE) is an infection of the endocardial surface of the heart. The intracardiac effects of this infection include severe valvular insufficiency, which may lead to intractable congestive heart failure and myocardial abscesses.

Infective endocarditis affects not only the heart, but also produces a wide variety of systemic signs and symptoms through several mechanisms, including both sterile and infected emboli and a variety of immunological phenomena.

Classification of Infective endocarditis: depending on the type of valve affected

1. ***Native valve endocarditis (NVE)*****:** endocarditis that may develop on natural valve. The affected valve may be damaged or normal.
2. ***Prosthetic valve endocarditis***: is when the endocarditis develops on prosthetic/'artificial' valve.
3. ***Endocarditis in intravenous drug abuser*** (IVDA).

- There is a marked rise in cases of prosthetic valve endocarditis and endocarditis in IV drug abusers in different parts of the world. However Native valve endocarditis is the commonest type of Infective endocarditis in Ethiopia and other developing countries.
- The classic clinical presentation and clinical course of IE has been characterized as either acute or subacute.
    - ***Acute Infective endocarditis***: frequently involves healthy valves. It is a rapidly progressive illness with destruction of valvular structures..

- ***Subacute Infective endocarditis***: typically affects only previously damaged valves. The course is insidious even in untreated cases which may extend over many months.

Etiologic agent of Infective endocarditis

- ***Streptococcus viridans*:** is a bacterium which is a normal flora of the oral cavity. It accounts for approximately 50-60% of cases of subacute infective endocarditis.
- **Group D streptococci:** the source for this bacterium is the gastrointestinal or genitourinary tract. Most cases infective endocarditis due to this organism is subacute.
- ***S. aureus*:** is the leading cause of Prosthetic valve endocarditis (PVE), acute infective endocarditis and endocarditis in IVdrug abusers. Approximately 35-60.5% of staphylococcal bacteremia is complicated by infective endocarditis. In more than half of cases endocarditis due to *S. aureus* occurs in the absence of underlying valvular disease. Mortality rate may range 40-50%
- ***Coagulase-negative* S. aureus:** it accounts for approximately 30% of PVE cases, fewer than 5% of NVE cases. It causes subacute disease
- ***HACEK*** organisms (i.e., *Haemophilus species, Actinobacillus, actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella species*) .These group of organisms usually cause subacute disease. It accounts for approximately 5% of infective endocarditis.
- ***Fungus:*** Mostly frequently cause subacute disease. *Candida albicans* is the commonest fungal etiology.

Pathophysiology:

All cases of infective endocarditis develop from a commonly shared process:

1. Bacteremia (nosocomial or spontaneous) that delivers the organisms to the valve's surface
2. Adherence of the organisms to valvular structures
3. Eventual invasion of the valvular leaflets and formation of vegetations.

- Infective endocarditis develops most commonly on the mitral valve, closely followed in descending order of frequency by the aortic valve, the combined mitral and aortic valve, the tricuspid valve, and, rarely, the pulmonic valve. Mechanical prosthetic and bioprosthetic valves exhibit equal rates of infection.

- Turbulence in blood flow damages valvular surface and edocardium which creates a favorable situation for formation of sterile thrombus (vegetation) made of platelets and fibrin.
- The microorganisms that most commonly produce endocarditis (i.e., *S. aureus; S.viridans;* group A, C, and Group D streptococci; enterococci) resist the bactericidal action of complement and possess fibronectin receptors for the surface of the fibrin and platelet thrombus.
- Either a spontaneous bacteremia or one that is the result of an invasive procedure gives access to the bacteria to adhere to the sterile platelet/fibrin vegetation. Most cases of subacute disease are secondary to the bactermias that develop from the activities of daily living (e.g., brushing teeth, bowel movements)
- The complications of acute bacterial endocarditis result from intracardiac disease and metastatic infection produced by suppurative emboli. Because of their shortened course, immunological phenomena are not a part of acute infective endocarditis.

Clinical Features

A. Subacute infective endocarditis

- The patient suspected of SBE should be asked about invasive procedures that may be causing bacteremia. Most subacute disease caused by *S.viridans* is related to dental disease.
- The symptoms of early subacute NVE usually are subtle and nonspecific.
- SBE is suggested by a history of a slowly progressive process characterized by fever, fatigue, anorexia, back pain, and weight loss.
- Less common developments are a cerebrovascular accident or congestive heart failure.
- When appropriate therapy is delayed for weeks or months, additional clinical features, embolic or immunological in origin, develop.

Embolic manifestations of infective endocarditis include:

- *Acute meningitis with sterile spinal fluid*
- *Hemiplegia due to embolization in the distribution of the middle cerebral artery*
- *Renal regional infarcts producing painless hematuria*
- *Splenic infarction*
- *Unilateral blindness caused by occlusion of a retinal artery*
- *Myocardial infarction resulting from embolization to a coronary artery.*

The risk of embolization is related to the type of the organism, the size of the vegetation and its rate of growth or resolution, and the location of the vegetation.

Immunologic Manifestations of SBE:

- Acute glomerulonephritis
- Osler's nodes
- Roth spots
- Presence of rheumatoid factor

Common Physical findings in SBE

- ***Fever:*** most patients have low grade fever; however 3-15% of patients with SBE may have normal or subnormal temperature.
- ***Murmurs***: the vast majority of patients have detectable heart murmurs (99% of cases). The absence of a murmur should cause clinicians to reconsider the diagnosis of IE. The major exception is right-sided infective endocarditis, in which only one third of cases have a detectable murmur.
- ***The peripheral lesions of subacute infective endocarditis*** are observed in only approximately 20% of patients as compared to 85% in the preantibiotic era.
  - ***Petechiae*** are the most common peripheral lesions. They may occur on the palpebral conjunctivae, the dorsa of the hands and feet, the anterior chest and abdominal walls, the oral mucosa, and the soft palate.
  - ***Subungual hemorrhages*** (i.e., splinter hemorrhages) are linear and red lesions that do not extend for the entire length of the nail.
  - ***Clubbing of fingers and toes*** may be seen. It primarily occurs in those patients who have an extended course of untreated infective endocarditis.
  - ***Arthritis*** associated with subacute infective endocarditis is asymmetrical and limited to 1-3 joints.
  - ***Splenomegaly*** is observed more commonly in patients with long-standing subacute disease. It may persist long after successful therapy.
  - ***Osler nodes*** are small tender nodules that range in color from red to purple and are located primarily in the pulp spaces of the terminal phalanges of the fingers and toes, soles of the feet, and the thenar and hypothenar eminences of the hands.

B. Acute infective endocarditis:

- History of antecedent procedures or illicit drug use must be investigated.

- Is a much more aggressive disease. The onset of illness is abrupt, with rapidly progressive destruction of the infected valve. The valvular leaflets are destroyed rapidly by bacteria that multiply very fast within the ever-growing friable vegetations.
- The clinical symptoms of acute infective endocarditis result from either embolic or intracardiac suppurative complications.
- There is an acute onset of high-grade fever and chills and a rapid onset of congestive heart failure.
- Complications develop within a week. These include the dyspnea and fatigue of severe congestive heart failure and a wide spectrum of neuropsychiatric complications resulting from involvement of the CNS.
- ***Roth spots*** are retinal hemorrhages with pale centers. The Litten sign represents cotton-wool exudates.
- ***Murmurs*** are present in nearly two third of patients with acute infective endocarditis. The most common type is murmur aortic regurgitation. Because of the rapid onset, the left ventricle does not have a chance to dilate. In this situation, the classic findings of increased pulse pressure that are seen in chronic AR are absent.
- ***Janeway lesions*** are irregular erythematous and painless macules (1-4 mm in diameter). They most often are located on the thenar and hypothenar eminences of the hands and feet. They usually represent an infectious vasculitis of acute infective endocarditis resulting from *S. aureus* infection.
- ***Acute septic monoarticular arthritis*** in patients with acute infective endocarditis most often is caused by *S aureus* infection.
- ***Purulent meningitis*** may be observed in patients with acute infective endocarditis , as compared to the aseptic type observed in patients with subacute disease.

C. ***Right-sided infective endocarditis:*** is associated with a very low rate of congestive heart failure and valvular perforation.

    - *Pulmonary infarcts may result from emboli of right-sided infective endocarditis*

Table III-4-1: Frequencies of Occurrence of prominent Clinical and Laboratory Manifestations in Endocarditis

Clinical manifestations	*% of occurrence*
Fever	> 95
Arthralgias and/or myalgias	25-45
Murmur	> 85
Splenomegaly	25-60
Splinter hemorrhages	20-40
Roth's spots	< 5
Osler's nodes	10-25
Janeway lesions	< 5
Clubbing	10-20
Clinically apparent emboli	25-45
Neurologic manifestations	20-40
LABORATORY MANIFESTATIONS	
Anemia	70-90
Leukocytosis	20-30
Proteinuria	50-65
Microscopic hematuria	30-50
Elevated serum creatinine level	10-20
Elevated erythrocyte sedimentation rate	>90
Rheumatoid factor	50
Circulating immune complexes	65-100
Decreased serum complement level	5-40

Diagnostic work up:

Lab Studies:

1. **Blood Culture :**
    - The gold standard test for the diagnosis of infective endocarditis is the documentation of a continuous bacteremia (>30 min in duration) through blood culture.

- For making diagnosing SBE draw 3-5 sets of blood cultures , at 3 different sites , over 24 hours.
- This detects 92-98% of cases in patients who have not received antibiotics recently.
- In the case of Acute infective endocarditis, 3 sets may be drawn over 30 minutes (with separate venipunctures) to document a continuous bacteremia.

2. Echocardiography

- Has become the indirect diagnostic method of choice, especially in patients who present with a clinical picture of infective endocarditis but who have nondiagnostic blood cultures.
- The diagnosis of infective endocarditis can never be excluded by a negative echocardiogram.

3. Other Tests:

- ***Electrocardiography*** may detect the 10% of patients who develop a conduction delay during infective endocarditis by documenting an increasing P-R interval.

Rheumatoid factor becomes positive in 50% of patients with subacute disease. It becomes negative after successful treatment.

Table III -4-2. The Duke Criteria for the Clinical Diagnosis of Infective Endocarditis

Major Criteria
1. Positive blood culture: for typical microorganism that causes infective endocarditis from two separate blood cultures. (*Viridans streptococci*, *Streptococcus bovis*, *HACEK group*, *or* Community-acquired *Staphylococcus aureus* or enterococci in the absence of a primary focus)
2. Positive echocardiogram:
• Definitive vegetation (oscillating intracardiac mass on valve or supporting structures)
• Abscess
• New partial dehiscence of prosthetic valve
• New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria
• ***Predisposition***: predisposing heart condition or IV drug abuse • ***Fever*** >38.0 °C. • ***Embolic phenomena***: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions • ***Immunologic phenomena***: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor • ***Microbiologic evidence***: positive blood culture but not meeting major criterion. ***Echocardiogram***: consistent with infective endocarditis but not meeting major criterion

SOURCE: Adapted from Durack et al.

Definitive Diagnosis can be made by documentation of:

- Two major criteria or
- One major and three minor criteria or
- Five minor criteria allows a clinical diagnosis of definite endocarditis.

Treatment:

All patients should be treated in the hospital to allow adequate monitoring of the development of complications and the response to the antibiotic therapy.

General measures:

- **Diet:** No special diets are recommended for patients with endocarditis; however, if the patient has congestive heart failure, sodium-restriction may be necessary.
- **Activity:** Activity limitations are determined by the severity of illness, complications (e.g., stroke), and the presence of significant congestive heart failure.

Medical Treatment

The major goals of therapy for infective endocarditis are

- Eradicating the infectious agent from the thrombus
- Treating the complications of valvular infection

1. Eradicating the infectious agent from the thrombus

- Antibiotics remain the mainstay of treatment for IE. In the setting of acute IE, antibiotic therapy should be instituted as soon as possible to minimize valvular

damage. Three to five sets of blood cultures should be obtained within 60-90 minutes, followed by the infusion of the appropriate antibiotic regimen.

- By necessity, the initial antibiotic choice is empiric, determined by clinical history and physical examination.
- In the case of subacute IE, treatment may be safely delayed until cultures and sensitivities are available. Waiting does not increase the risk of complications in this form of the disease.
- Eradicating bacteria from the fibrin-platelet thrombus is extremely difficult..
- Intravenous administration is the preferred to ensure reliable serum therapeutic levels.
- The antibiotics should be bactericidal and are should be administered at higher dose for prolonged period of time.

Empirical antibiotic treatment

NVE of sub acute nature:

- Crystalline penicillin 3-4 million IU IV every 4 hours for 4- 6 weeks plus
- Gentamicin 1mg/kg (80 mg) IV TID for 2 weeks plus

Prosthetic Valve endocarditis:

- Vancomycin 1gm IV BID for 6 weeks Plus
- Gentamicin 1mg/kg (80 mg) IV TID for 2 weeks plus
- Refampicin 300 mg PO /TID for 6 weeks

Acute Infective endocarditis where S.aureus is suspected: E.g. hospital acquired infection

- Naficillin 1.5-2gm IV every 4 hours OR Vancomycin 1gm IV BID for 6 weeks Plus
- Gentamicin 1mg/kg (80 mg) IV TID for 2 weeks.

When the result of blood culture is made available the choice of antibiotics depend on the type of organism identified and the anti microbial sensitivity.

2. Dealing with the complications of valvular infection. The latter includes both the intracardiac and extracardiac consequences of infective endocarditis.

- Mild congestive heart failure resulting from valvular insufficiency or myocarditis may be managed with standard medical therapy for CHF.
- Although thrombosis is a key element of infective endocarditis, anticoagulation with heparin or Warfarin is controversial, and it should be avoided.

Surgical Treatment: Approximately 15-25% of patients with IE eventually require surgery.

Indication for Surgery:

- *Acute AR with severe Heart failure*
- *Fungal endocarditis*
- *Mobile vegetation > 10mm in size.*
- *Evidence of valve ring or myocardial abscess*
- *Recurrent embolization despite adequate antibiotic therapy*
- *Poor response to antibiotics*
- *Prosthetic valve dysfunction associated with CHF*
- *Valve ring Abscess near a prosthetic valve*

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Infective endocarditis , pages 731-739.

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5. Cardiomyopathy

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define Cardiomyopathy.*
2. *List the etiologies of Cardiomyopathies.*
3. *Describe the different types of Cardiomyopathies.*
4. *Understand the Epidemiology of Cardiomyopathies.*
5. *Describe the pathogenesis of Cardiomyopathies.*
6. *Identify the clinical manifestation of Cardiomyopathies.*
7. *Understand the diagnostic approach of Cardiomyopathies.*
8. *Understand the management of patients Cardiomyopathies.*

Definition:

Cardiomyopathies are a group of diseases that affect the myocardium and are not the result of hypertension, valvular, coronary or pericardial abnormalities. Cardiomyopathies are frequently associated with myocardial dysfunction and subsequently heart failure. With few exceptions, histologic findings are nonspecific, with myocyte hypertrophy, cellular necrosis, and fibrosis.

Etiologic classification of Cardiomyopathies:

Primary Myocardial Involvement

- ***Idiopathic***
- ***Familial***
- ***Eosinophilic endomyocardial diseases***
- ***Endomyocardial Fibrosis***

Secondary myocardial involvement:

- ***Infective*** Myocarditis: Viral , bacterial , fungal , protozoal , Metazoal , Spirochetal
- ***Metabolic :*** Thyrotoxicosis
- ***Familial storage diseases:*** Glycogen storage diseases , Hemochromatosis ,
- ***Deficiencies :*** Electrolyte , Nutritional (Vitamin B_1 deficiency)
- ***Connective tissue diseases :*** SLE , polyarteritis nodosa , Rheumatoid arthritis , Systemic sclerosis
- ***Infiltration and granulomas ;*** Amyloidosis , sarcoidosis , malignancies
- ***Neuromuscular :*** muscular dystrophies ,myotonic dystrophies

- ***Sensitivity and toxic reactions :***Alcohol , drugs , radiation
- ***Peripartum heart diseases***

Table III-5-1 Clinical classification of Cardiomyopathies

DISORDER	***DESCRIPTION***
Dilated cardiomyopathy	Dilatation and impaired contraction of the left or both ventricles. Caused by familial/genetic, viral and/or immune, alcoholic/toxic, or unknown factors, or is associated with recognized cardiovascular disease.
Hypertrophic cardiomyopathy	Left and/or right ventricular hypertrophy, often asymmetrical, which usually involves the interventricular septum. Mutations in sarcoplasmic proteins cause the disease in many patients.
Restrictive cardiomyopathy	Restricted filling and reduced diastolic size of either or both ventricles with normal or near-normal systolic function. Is idiopathic or associated with other disease (e.g., amyloidosis, endomyocardial disease).

5.1 Dilated Cardiomyopathy

Definition

- This condition may be defined as impaired left and/or right ventricular systolic dysfunction characterized by an ejection fraction <40% in the presence of increased left ventricular dimensions (left ventricular end-diastolic size >115% of that calculated for age and body surface area).

Pathophysiology

- Dilated cardiomyopathy represents the final common morphologic outcome of a variety of biological insults. It is a combination of myocyte apoptosis and necrosis with increased myocardial fibrosis, producing reduced mechanical function. Many causes are a result of direct toxicity (e.g., alcohol) or mechanical insults (e.g., chronic volume overload in mitral valvular regurgitation), infection (eg myocarditis).

Clinical manifestations

- A careful history is essential , with particular emphasis on
    - Family history of similar illness
    - Exposure to cardio toxins such as alcohol
    - Protracted "flu-like illness" or respiratory tract infection may suggest previous myocarditis
    - History of recent delivery or being in the last trimester of pregnancy
- Some patients may have left ventricular dilatation for months or even years and may remain asymptomatic and are diagnosed only by screening or postmortem examination.
- Symptoms of left and right sided congestive heart failure develop gradually in most patients. Unfortunately, the most common clinical presentation is one of progressive deterioration, with worsening heart failure and death occurring over a variable time course.
- Syncope may result from arrhythmias
- Systemic embolization, often emanating from ventricular thrombus, may occur.

Physical examination:

- Hypotension , tachycardia
- Cardiomegaly (displaced PMI)
- Findings of CHF : narrow pulse pressure , raised JVP and S_3 and S_4 gallops

- Functional mitral or tricuspid regurgitation.

Diagnostic work up:

- ***Chest radiograph***: enlargement of cardiac silhouette and evidence of pulmonary congestion
- ***ECG***: sinus tachycardia or atrial fibrillation , , ventricular arrhythmias, St segment and T wave abnormalities
- ***Echocardiogram:*** Left ventricular dilatation and dysfunction (ejection fraction < 40 %)
- ***Other laboratory investigation include***
    - Complete blood cell count
    - Renal function test
    - Blood glucose (fasting or random)
    - Lipid profile glucose
    - Thyroid function tests

Treatment of Dilated Cardiomyopathy

Medical Therapy: Standard therapy of heart failure

- Salt restriction
- Diuretics
- Digitalis
- ACE inhibitors or Angiotensin II receptor blockers
- Spirinolactone
- Alcohol should be avoided
- Identify and treat the underlying cause if it is treatable

Surgical Therapy: Cardiac transplantation provides a median 10-year survival and is effective palliation in appropriately selected individuals.

Prognosis.

- In the absence of a specific remediable etiology (e.g., in peripartum cardiomyopathy, alcoholic cardiomyopathy, ischemic hibernating revascularizable myocardium), the overall outcome is poor in patients with cardiomyopathy.
- Majority of patients have downhill course, and particularly those >55 years, die within 3 years of onset of symptoms. The 5-year survival rate of patients diagnosed with heart failure is 50%.
- Blacks are more likely to suffer progressive heart failure and death than whites

5.2 Hypertrophic Cardiomyopathy

Definition:

Hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy (myocardial thickness greater than 1.5 cm), typically of none dilated chamber, without obvious causes. Other etiologies of left ventricular hypertrophy, such as long-standing hypertension and aortic stenosis need to be excluded before one can diagnose HCM.

Genetic Predisposition:

- HCM is the most common genetic cardiovascular disease. About half of patients with HCM have a positive family history with autosomal dominant transmission.
- The prevalence in the general adult population for people with phenotypic evidence of HCM is estimated at 1 per 500.

Pathophysiology:

Generally, ventricular hypertrophy involves the proximal portion of the interventricular septum. As the septum thickens, it may narrow the outflow tract. In addition, systolic anterior motion of the mitral valve may occur and result in left ventricular outflow tract obstruction and mitral regurgitation. When systolic anterior motion occurs, the mitral valve leaflets are pulled or dragged anteriorly toward the ventricular septum, producing the obstruction. Consequently, the left ventricle has to generate much higher pressures to overcome the out flow obstruction and to pump blood to the systemic circulation. Premature closure of the aortic valve may occur and is caused by the decline in pressure distal to the left ventricular outflow obstruction.

Clinical Features

- The clinical course of HCM is variable. Most patients with HCM are asymptomatic.
- The most common symptom of HCM is dyspnea on exertion.
- Patients may also complain of chest pain with exertion, syncope or near syncope, or palpitations.. Congestive heart failure and atrial fibrillation along with their accompanying symptoms may be part of the natural history of HCM.
- Unfortunately, the first clinical manifestation of the diseases may be sudden cardiac death frequently occurring in young children and young adults. , often during or after physical exertion.

Physical examination:

- Unless congestive heart failure has developed, the lungs are usually clear and the jugular venous pressure normal
- ***Bisferiens pulse***: rapidly rising carotid pulse followed by a collapse in the pulse and then a secondary rise.
- ***The point of maximal impulse*** may be double or triple, forceful and sustained.
- ***S4 gallop*** may be present.
- ***Systolic murmur***: *t*he classic auscultatory finding for HCM is a crescendo-decrescendo systolic murmur along the left sternal border that increases with the Valsalva maneuver. In young adults, HCM is the most common etiology for sudden cardiac death.

Diagnosis

Laboratory studies generally will be unremarkable.

- ***Chest radiograph*** may suggest left ventricular hypertrophy but will often be normal because the hypertrophy in HCM involves the ventricular septum.
- ***The electrocardiogram*** often shows left ventricular hypertrophy and occasionally may also have a pseudoinfarct pattern. Left atrial abnormality may be present if the patient has had long-standing mitral regurgitation from systolic anterior motion of the mitral valve. Atrial fibrillation also may be present as one of the complications of HCM.
- ***Echocardiography*** is the gold standard for diagnosing HCM. On transthoracic echocardiography, the clinician should note the thickness of the septum; location and pattern of hypertrophy; site and degree of left ventricular outflow tract obstruction; presence of systolic anterior motion of the mitral valve; presence of premature closure of the aortic valve; and any change in severity of obstruction with amyl nitrite

Treatment:

Medical Therapy

- Competitive sport and probably strenuous exercise should be avoided.
- Dehydration should be avoided and diuretics should be used with caution.
- ß-blockers are considered first-line therapy. By decreasing contractile force, ß-blockers decrease the outflow gradient and decrease oxygen demand. ß-blockers also lengthen diastolic filling by slowing the heart rates. They help to control chest pain.
- Calcium channel blocker: Second-line therapy includes the verapamil and, Diltiazem can be used. But Nifedipine, amlodipine and felodipine should be avoided because they

cause peripheral vasodilatation, which may result in decreased left ventricular filling and worsening of symptoms of outflow tract obstruction.

- Atrial fibrillation is a common complication of HCM. Treatment of persistent atrial fibrillation in HCM includes anticoagulation and rate control, preferably with ß-blockers.
- Digoxin should be avoided in HCM patients, particularly in those with resting or latent obstruction, because of its positive inotropic effect.
- Patients with HCM should receive prophylactic antibiotics for endocarditis prevention before dental or invasive procedures. Turbulent flow through the LVOT striking the aortic valve as well as mitral regurgitation from systolic anterior motion of the mitral valve predispose to endocarditis.

Surgical Therapy

- Septal myomectomy/myotomy may cause lasting symptomatic relief in ¾ of severely symptomatic patients.
- Alcohol ablation: ethanol injection in to the septal artery has also been reported to reduce obstruction.

Prevention*:* First degree relatives of patients with HCM should be screened with ECHO.

Restrictive Cardiomyopathy

Definition

- Restrictive cardiomyopathy is a disease of the myocardium that is characterized by restrictive filling and reduced diastolic volume of either or both ventricles with normal or near-normal systolic function.

Pathophysiology:

These conditions result in impaired ventricular filling and primarily diastolic heart failure. They present with a clinical heart failure syndrome that is frequently indistinguishable from that caused by systolic dysfunction. Atrial fibrillation is poorly tolerated. It simulates other right side heart failure like cor pulmanale and diastolic dysfunction of constricted pericarditis.

Clinical Features:

- Exercise intolerance and dyspnea are the prominent symptoms.
- Peripheral edema with predominant ascites
- Enlarged tender and pulsatile liver.
- JVP is elevated and it doesn't fall normally during inspiration (Kussmaul's sign)
- The heart sounds may be distant but apical impulse is easily palpable unlike in constrictive pericarditis.

Differential Diagnosis: The clinical features are very similar to constrictive pericarditis.

Diagnostic work up

- ***Chest x-ray :*** mild cardiac enlargement
- ***ECG:*** low voltage and conduction defects
- ***Echocardiography:*** Increases left ventricular wall thickness, normal or mildly reduced systolic function.

6. Myocarditis

Learning objectives: *at the end of this lesson the student will be able to:*

1. *Define Myocarditis. .*
2. *List the etiologies of Myocarditis.*
3. *Describe the different types of Myocarditis.*
4. *Understand the epidemiology of Myocarditis.*
5. *Understand the pathophysiology of Myocarditis.*
6. *Identify the clinical manifestation of Myocarditis.*
7. *Identity consequences of Myocarditis.*
8. *Understand the diagnostic approach of Myocarditis.*
9. *Understand the principle of management of Myocarditis.*

Definition: Myocarditis is inflammation of the myocardium often resulting from infectious process, which subsequently leads to myocardial destruction and a dilated cardiomyopathy. The acute picture is nonspecific unless overt congestive heart failure develops. Although the causes of myocarditis are numerous, the most common association is an antecedent viral syndrome.

Etiologies of Myocarditis

1. ***Infectious causes***
    - Viral infections : Coxsackievirus B , HIV myocarditis (overt involvement is seen in 10 % of HIV patients)
    - Bacterial myocarditis:
        - Not common usually occurs as a complication of infective endocarditis.
        - Diphtheric myocarditis may develop in ¼ of patients with diphtheria
    - Fungal myocarditis
    - Protozoal myocarditis: Chaga's disease caused by a protozoon Trypanosoma cruzi and transmitted by an insect vector. It is one of the most common causes of heart disease in Central and South America.
    - Rickettsial myocarditis :associated with Typhus , Lyme disease
    - Spirocheatal myocarditis: associated with Relapsing fever.

2. ***Hypersensitivity and toxic reactions to :***
    - Drugs : Doxorubicin (anti- neoplastic agent)
    - Radiation
3. ***Giant cell myocarditis*** : is a rare form of myocarditis of unknown etiology

Pathophysiology:

Myocarditis is defined as inflammatory changes in the heart muscle and is characterized by an interstitial mononuclear cell infiltrate with an attendant myocyte necrosis.

It is not known whether the infiltrate is caused by a direct invasion of the infective agents or by a systemic immune response. In the chronic stage, cytotoxic T lymphocytes infiltrate the myocardium and mediate an autoimmune response with myocardial autoantibody activity directed against cardiac myosin. This autoimmune process persists after the viral particles are no longer detected. Coronary artery thrombus formation, luminal obstruction, ischemia, and dysrhythmias compound the deleterious effects of the inflammatory response.

Clinical features

- The clinical presentation of myocarditis is variable. Patients may present with a nonspecific illness characterized by fatigue, mild dyspnea, or fulminant congestive heart failure (CHF). Myocarditis may even cause sudden death in some patients.
- The majority of cases of myocarditis are subclinical; therefore, the patient rarely seeks medical attention during acute illness.
- An antecedent viral syndrome has been documented in 60% of patients with myocarditis. The typical time interval between the onset of the viral illness and cardiac involvement is 2 weeks.
- Fever is present in 20% of cases. Fatigue , myalgia and,malaise are common symptoms
- Chest pain or chest discomfort is reported in 35% of cases. The chest pain is often pleuritic quality with precordial pain of a sharp stabbing nature. Sometimes it may be substernal and squeezing, more typical of ischemic pain.
- Dyspnea on exertion is common and orthopnea and shortness of breath at rest may be noted if CHF is present.
- Palpitations are common.
- Syncope signals development of AV block or malignant dysrhythmias and may lead to sudden death in patients with myocarditis.

Physical examination:

- Patients with mild cases of myocarditis have a nontoxic appearance and simply may appear to have a viral syndrome. Tachypnea and tachycardia are common. Tachycardia is often out of proportion to fever.
- More acutely ill patients have signs of left ventricular failure including:
    - Raised JVP, bilateral basal crepitations on the chest, ascites and pperipheral edema. S_3 gallop may be noted with significant cardiac enlargement (displaced apical impulse). S_1 is soft or muffled. Cyanosis may be noticed.
    - Hypotension caused by left ventricular dysfunction is uncommon in the acute setting. A poor prognosis is indicated when hypotension is present.
    - Cardiogenic shock is observed in fulminant cases and has a high mortality.
    - Murmurs of mitral or tricuspid regurgitation may be present due to ventricular dilation.
- In cases where a dilated cardiomyopathy has developed, signs of peripheral or pulmonary thromboembolism may be found.
- Associated pericarditis may manifest with a pericardial friction rub. Pericardial effusion is common, but signs of tamponade (e.g., hypotension, jugular venous distention, muffled heart sounds) are rare.
- Pleural friction rub might be heard because pleuritis can occur with cases of acute myocarditis.

Diagnostic workup

Since many cases of myocarditis are not clinically obvious, a high degree of suspicion is required for the making a diagnosis of acute myocarditis.

Laboratory Studies:

- Erythrocyte sedimentation rate (ESR) is elevated in 60% of patients with acute myocarditis.
- Leucocytosis is present in 25% of cases.

Imaging Studies:

- **Chest x-ray:** often reveals a normal cardiac silhouette, but pericarditis or overt clinical CHF may be associated with cardiomegaly. Vascular redistribution, interstitial and alveolar edema and pleural effusion may also be noticed.
- ***Echocardiography:*** Dilated chambers and reduced ejection fraction indicating left ventricular systolic dysfunction.
- ***ECG:*** Sinus tachycardia is the most frequent finding. ST-segment elevation without reciprocal depression, particularly when diffuse, is helpful in differentiating myocarditis from acute myocardial infarction

Treatment of Myocarditis

- Patients with mild symptoms and no signs of cardiac failure or dysrhythmia may be treated on an outpatient basis.
  - The medical treatment of myocarditis is directed towards amelioration of associated complications including CHF and cardiogenic shock, arrhythmias, and thromboembolism.

1. ***Left ventricular dysfunction with signs of CHF should be treated with;***
   - Low sodium diet
   - Limitation or avoidance of exercise as exercise may have deleterious effect.
   - Diuretics
   - Digoxin: should be given with caution as patients with myocarditis are sensitive for digitalis toxicities.
   - ACE inhibitors and vasodilators
   - In general, sympathomimetic and beta-blocker drugs should be avoided because they increase the extent of myocardial necrosis and mortality.
2. ***Arrhythmias :***
   - Detection of dysrhythmia with inpatient cardiac monitoring.
   - Medical therapy for arrhythmias
   - Implantation of cardiac pacemakers.
3. ***Avoiding risk of thromboembolism:;***
   - Anticoagulants such as Warfarin or Heparin may be given.
   - Nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in the early course of disease because of inhibition of prostaglandin production, worsened myocyte function, and increased myocardial necrosis.

Prognosis:

- Majority of cases are believed to be clinically silent and resolve spontaneously without sequelae; therefore, it is difficult to make accurate statements concerning the prognosis of myocarditis.
- Patients presenting with CHF experience morbidity and mortality based on the degree of left ventricular dysfunction, and the presence of arrhythmias and thromboemblic complications increase the risk of mortality from myocarditis.

References:

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EPHTI
Ethiopia Public Health Training Initiative

7. Hypertension.

Learning objectives: *at the end of this lesson the student will be able to:*

1. *Define Hypertension.*
2. *List the etiologies of Hypertension.*
3. *Describe the different types of Hypertension.*
4. *Understand the epidemiology of Hypertension.*
5. *Understand the pathophysiology of Hypertension.*
6. *Identify the clinical manifestation of Hypertension.*
7. *Identity consequences of Hypertension.*
8. *Understand the diagnostic approach of Hypertension.*
9. *Understand the management of chronic hypertension and hypertensive crisis.*

Definition:

- Hypertension is defined as arterial blood pressure that exceeds 140/90mmHg at several determinations. This is an arbitrary definition because a diastolic pressure of even 85 mm Hg may be associated with increased cardiovascular morbidity and mortality.
- Hypertension is one of the most common diseases afflicting humans throughout the world. Because of the associated morbidity and mortality and the cost to society, hypertension is an important public health challenge.
- It is easily detectable, usually easily treatable, and often leads to lethal complications if left untreated.
- Hypertension is the most important modifiable risk factor for coronary heart disease, stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease. Therefore, health care professionals must not only identify and treat patients with hypertension but also promote a healthy lifestyle and preventive strategies to decrease the prevalence of hypertension in the general population.

Epidemiology

- Overall, approximately 20% of the world's adults are estimated to have hypertension in excess of 140/90 mm Hg. Some studies done in developed countries show almost 50 % of the population may have hypertension.
- The prevalence dramatically increases in patients older than 60 years.
- The prevalence is higher among balks than whites.

- The age-adjusted prevalence of hypertension is slightly higher in men than in women. The prevalence in women is closely related to age, with substantial increase occurring after age 50. This may be related to hormonal changes associated with menopause.
- There is paucity of data about prevalence of hypertension in Ethiopia , however some studies have shown that 6% of adolescent and young adults in urban area may have hypertension, and 11% of immigrant from Ethiopia to Israel , after 2- 4 years of stay were found to have developed hypertension

Classification

Because the risk to an individual patient may correlate with the severity of hypertension, a classification system is essential for making decisions about aggressiveness of treatment or therapeutic interventions.

Table III-7-1. Classification of blood pressure for adults and older children *

	BLOOD PRESSURE (in mm Hg)		
CATEGORY	***Systolic***		***Diastolic***
Optimal	<120	and	<80
Normal	<130	and	<85
High-normal	130–139	or	85–89
Hypertension			
Stage 1	140–159	or	90–99
Stage 2	160–179	or	100–109
Stage 3	≥ 180	or	N ≥ 110

- When systolic and diastolic blood pressure levels fall into different categories, the higher category should be selected to classify the individual's blood pressure status.

  E.g. 160/92 mm Hg should be classified as stage 2 hypertension

  174/120 mm Hg should be classified as stage 3 hypertension.

- Isolated systolic hypertension is defined as systolic blood pressure 140 mm Hg or greater and diastolic blood pressure less than 90 mm Hg and staged approximately (e.g., 170/82 mm Hg is defined as stage 2 isolated systolic hypertension).
- In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify the presence or absence of target organ damage and additional risk factors. This specificity is important for risk classification and treatment.
- Optimal blood pressure with respect to cardiovascular risk is ≤ 120/80 mm Hg.
- Hypertension should be diagnosed based on the average of two or more readings taken at each of two or more visits after an initial screening.

The natural history of essential hypertension:

- It evolves from occasional to established hypertension. After a long invariable asymptomatic period, persistent hypertension develops into complicated hypertension, in which target organ damage to the aorta and small arteries, heart, kidneys, retina, and central nervous system is evident.
- The progression begins with prehypertension in persons aged 10-30 years (by increased cardiac output) to early hypertension in persons aged 20-40 years (in which increased peripheral resistance is prominent) to established hypertension in persons aged 30-50 years, and, finally, to complicated hypertension in persons aged 40-60 years.

Etiologic Classification of Hypertension: Hypertension may be classified as either essential or secondary.

I. Primary or essential hypertension (90-95%):

- Essential hypertension is diagnosed in individuals in whom generalized or functional abnormalities may be the cause of hypertension but no specific secondary causes are identified.
- The pathophyisoliogy of essential hypertension is multifactorial and highly complex. A number of factors modulate the blood pressure. These factors include humeral mediators, vascular reactivity, circulating blood volume, vascular caliber, blood viscosity, cardiac output, blood vessel elasticity, and neural stimulation.

Some factors that may contribute for the development of essential hypertension include:

- ***Genetic predisposition***: the exact mechanism has not been established
- ***Environment***: a number of environmental factors have been implicated
    - Dietary salt intake and Salt sensitivity
    - Obesity
    - Occupation
    - Family size and crowding
- ***Pregnancy-induced hypertension:*** Toxemia of pregnancy

II. Secondary causes of hypertension:

In 5-10 % of patients with hypertension, the hypertension is secondary to an identifiable disorder.

A. ***Renal Hypertension*** **(2.5-6%)** a variety of renal diseases may be accompanied by hypertension

- ***Renal parenchymal disease*** :
    - Chronic pyelonephritis
    - Acute and chronic glomerulonephritis
    - Polycystic kidney disease
    - Urinary tract obstruction
    - Renin-producing tumor
- ***Renovascular hypertension*** (0.2-4%)
    - Coarctation of aorta
    - Vasculitis
    - Collagen vascular disease

B. ***Endocrine (1-2%)*** –

- Oral contraceptives
- Adrenocoritical hypertension
    - Primary aldosteronism
    - Cushing syndrome
    - Congenital adrenal hyperplasia
- Pheochromocytoma
- Acromegally

- Myxoedema
- Thyrotoxicosis

C. *Neurogenic :*

- Psychogenic
- Increased intracranial pressure
- Acute spinal cord section

D. Drugs and toxins

- Alcohol
- Adrenergic medications

Consequences of Hypertension (End organ /target organ damage)

Patients with hypertension die prematurely, the most common cause of death is heart disease, with stroke and renal failure also frequent, particularly in patients with retinopathy

1. Effects on the Heart :

- Left ventricular hypertrophy as a compensatory mechanism
- Coronary artery disease /Ischemic heart disease:
  - Angina Pectoris
  - Myocardial infarction which may lead to heart failure

2. Neurologic effects

a. Retinal changes :

i. Exudates: hard and soft exudates

ii. Hemorrhages: dot and bloat hemorrhages

iii. Thickening of arterioles – copper wiring → silver wiring

iv. Abnormalities on arteriolo –venular crossings (A/V crossings)

v. Papilledema

b. Central nervous system dysfunction

i. Cerebrovascular disease

- Transient ischemic attacks : episodic dizziness , unilateral blindness , hemiparesis etc
- Stroke
  - Ischemic stroke : due to atherosclerosis of cerebral blood vessels

- Hemorrhagic stroke: as a result of elevated arterial pressure and formation of vascular micro- aneurysms.

ii. ***Hypertensive encephalopathy***: consists of severe hypertension, altered state of consciousness, increased intracranial pressure with papilledema and seizure. Focal neurologic deficits are not common.

3. ***Effects on the kidneys*** :
   - Arteriolosclerosis of the afferent and efferent arterioles and the glumerular capillary tuft impairs renal function. Patients may have proteinuria and microscopic hematuria and later on develop chronic renal failure.

Risk factors for an adverse prognosis in hypertension:

- Black race
- Youth
- Male sex
- Smoking
- Diabetes mellitus
- Hypercholesterolemia
- Obesity
- Excess alcohol intake
- Evidence or of end organ damage

Approach to a patient with Hypertension:

Diagnosis of hypertension*:* is confirmed after an elevated blood pressure ≥ 140/90 mm Hg, properly measured, has been documented on at least 3 separate occasions (based on the average of 2 or more readings taken at each of 2 or more visits after initial screening).

An accurate measurement of blood pressure is the key to diagnosis.

- Several determinations should be made over a period of several weeks.
- At any given visit, an average of 3 blood pressure readings taken 2 minutes apart using a mercury manometer is preferable.
- Blood pressure should be measured in both the supine and sitting positions, auscultating with the bell of the stethoscope.

- On the first visit, blood pressure should be checked in both arms and in one leg to avoid missing the diagnosis of coarctation of aorta or subclavian artery stenosis.
- As the improper cuff size may influence blood pressure measurement, a wider cuff is preferable, particularly if the patient's arm circumference exceeds 30 cm.
- The patient should rest quietly for at least 5 minutes before the measurement.
- Although somewhat controversial, the common practice is to document phase V (a disappearance of all sounds) of Korotkoff sounds as the diastolic pressure.

Patient evaluation*: *In evaluating a patient with hypertension the initial history, physical examination and laboratory should be directed at

1) *Establishing pretreatment base line hypertension :*
2) *Identifying correctable secondary caused of hypertension*
3) *Determining if target organ damage is present: patients may have undiagnosed hypertension for years without having had their blood pressure checked. Therefore, a search for end organ damage should be made through proper history and physical examination.*
4) *Determining whether other cardiovascular risk factors are present*
5) *Assessing factors that may influence the type of therapy or be changed adversely by therapy*

Clinical symptoms and History:

- Most patients with hypertension have no specific symptoms and are identified only in the course of physical examination
- If patients develop symptoms, the they may be attributable to
  - The elevated BP itself or
  - The end organ damage associated with hypertension or
  - The underlying secondary disease

Some of the symptoms may be

- ***Headache:*** though popularly considered symptom of high BP, it is a characteristic of only sever hypertension. Such headaches are localized to the occipital region and present when the patient awakens in the morning but subsides spontaneously after several hours
- ***Dizziness , palpitation , easy fatigability and impotence***
- ***Symptoms referable to vascular diseases or evidences of target organ damage include***

- Epistaxiis , hematuria
- Retinal changes→blurring of vision
- Cerebrovascular damages : Transient ischemic attacks → episodes of weakness or dizziness or Stroke may occur (hemorrhagic or ischemic)
- Cardiovascular damages : chest pain /angina pectoris or myocardial infarction which may cause dyspnea due to heat failure
- Pain due to dissecting aorta

Symptoms/history suggesting underlying disease

- A history of known renal disease, abdominal masses, anemia, and urochrome pigmentation.
- A history of repeated UTI may suggest chronic pylonephritis.
- A history of sweating, labile hypertension, headache, nervousness, postural dizziness, palpitations and weight loss may suggest the diagnosis of pheochromocytoma.
- A history of polyuria, polydiepsia and muscle weakness may be to secondary to hypokalemia associated with aldosteronism.
- A history of weight gain , emotional labiality may suggest Cushing's syndrome
- A history of cold or heat tolerance, sweating, lack of energy, and bradycardia or tachycardia may indicate hypothyroidism or hyperthyroidism.
- A history of drug ingestion, including oral contraceptives, licorice, and sympathomimetics, should be looked for.

Predisposing factors for hypertension

- Strong family history of hypertension
- Age : secondary hypertension often develops before the age of 35 or after 55

Associated cardiovascular risk factors:

- Cigarette smoking
- Lipid abnormality or hypercholesterolemia,
- Diabetes mellitus
- Family history of early deaths due to cardiovascular diseases
- Alcoholism.

- Obtain a history of over-the-counter medication use, current and previous unsuccessful antihypertensive medication trials

Physical Examination:

- **General appearance:**
  - Round face and truncal obesity suggests Cushing syndrome
  - Muscular development in the upper extremities out of the proportion of the lower extremities suggests coarctation of the aorta
- ***Proper measurement of blood pressure***
  - Compare the BP and pulses in the two upper extremities and in supine and standing position
  - A rise in diastolic pressure when the patient goes from supine to standing position is most compatible with essential hypertension while a fall in BP in the absence of antihypertensive medications suggests secondary hypertension.
- ***Funduscopic evaluation of the eyes***: should be performed to detect any evidence of hypertensive retinopathy. Some of the findings may be flame-shaped hemorrhages and cotton wool exudates. The presence of papilledema and other neurologic signs raises the possibility of increased intracranial pressure
- ***Palpation of all peripheral pulses should be performed***. Mainly palpation and auscultation of carotid arteries. Femoral pulse should be felt and compared with radial pulse. Radio femoral delay suggests Coarctation of the aorta.
- ***A careful cardiac examination:*** is performed to evaluate signs of LVH. These include displacement of apex, a sustained and enlarged apical impulse, and the presence of an S_4. Occasionally, a tambour S_2 is heard with aortic root dilatation.
- ***Abdominal examination:***
  - Look for renal artery bruit over the upper abdomen; the presence of a unilateral bruit with both a systolic and diastolic component suggests renal artery stenosis.
  - Palpate for an abdominal aneurysm, enlarged kidneys of polycystic kidney diseases.

Diagnostic workup

Laboratory investigations:

Unless a secondary cause for hypertension is suspected, only the following routine laboratory studies should be performed:

- CBC and Hematochrite
- Urinalysis including microscopy , protein , blood and , glucose
- Fasting blood glucose
- Serum electrolytes : serum K^+
- Lipid profile (total cholesterol, low-density lipoprotein [LDL] and high-density lipoprotein [HDL], and triglycerides).
- Serum creatinine, uric acid,
- ECG

Imaging Studies:

- ***Echocardiography***: to detect LVH

Special studies to screen for Secondary hypertension: should be requested only when secondary hypertension is strongly suspected.

- ***Renovascular disease*** : ultrasound and Doppler flow study
- ***Pheochromocytoma*** : 24 hrs urine assay of metanehprines and catecholamine
- ***Cushing's syndrome***: overnight dexamethason suppression test or 24 hrs urine cortisol
- ***Primary aldosteronism***: plasma aldostrone
- ***Thyrotoxicosis or Myxoedema*** : Thyroid function test (TSH , T_3 and T_4)

Therapy of Hypertension

Indication for treatment:

- Patients with a diastolic pressure >90mm Hg or systolic pressure > 140 mm Hg repeatedly
- Isolated systolic hypertension (systolic BP > 160 with diastolic BP < 89 mmHg) if the patient is older than 65 years.

Goal of therapy :

- *Reducing the diastolic BP to < 90 mmHg and systolic BP < 150mmHg.*

1. ***General measures : non pharmacologic therapy***

a. ***Sodium restriction***: intake not more than 100 mmol/d (2.4 g sodium or 6 g sodium chloride).

b. ***Lifestyle modifications***.

- Weight reduction in obese patients
- Limitation of alcohol intake : alcohol potentiates the action of catecholamines and may exacerbate hypertension
- Regular physical exercise: increase aerobic activity (30-45 min most days of the week).
- Maintain adequate intake of dietary potassium, calcium and magnesium for general health. (healthy diet like fruits, vegetables, etc)
- Stop smoking
- Reduce intake of dietary saturated fat and cholesterol

2. ***Pharmacologic therapy***.

A. *Diuretics* : are often the first line drugs , and reduce extra cellular fluid volume

- ***Thiazide diuretics*** : are more effective anti-hypertensive agents than loop diuretics

Dose: Hydrochlorothiazide 25 mg PO daily and may be increased gradually

Side effects: hypokalemia, hyperuricemia, hyperglycemia

Contraindcation: Gout

- ***Potassium-sparing diuretics (e.g. Spironolactone)*** : is a competitive inhibitor of aldosteron and may be used in primary hyperaldosteronism (as an additional therapy in combination with thiazide diuretics)

Dose: 25-50 mg PO 2 to 4 times daily

B. *β-adrenergic blocking agents* : reduce cardiac output and rennin release

- **β-blockers :** Propanolol , Metoprolol , Labetolol , Carvidolol , Atenolol

Doses: Propranolol 20 mg PO /day to Maximum of 120 mg PO 4X/day

Metoprolol: 25 – 150 mg PO BID

Atenolol: 25-100 mg PO/day

Side effects: bronchospasm, bradycardia, worsening of heart failure, impotence, depression

Contraindication: Asthma, peripheral vascular disease (severe)

C. ***Centrally acting agents***: These agents inhibit sympathetic out flow from the CNS.

- ***Methyldopa*** : 250 mg -1000 mg PO BID , TID or QID

  Side effects: postural hypotension, depression, gyneacomastia.

D. ***Vasodilators:*** dilate arteriols and arteries, reducing peripheral vascular resistance which inturn reduces high blood pressure.

- ***Hydrallazine*** : Oral 10-75 mg PO QID

  Paraneteral: 10-50 mg IV or PO every 6 hours.

  Side effects: – headache, lupus erythromatosis like syndrome
- ***Minoxidil*** : 2.5 -40 mg PO BID

Side effects: Orthostatic hypotension

E. ***Calcium channel blockers***: by modulating calcium release in smooth muscles, calcium channel blockers reduce smooth muscle tone, resulting vasodilatation.

Dihydropyridines: Nifedipine, Felodipine, Amlodipine

Non dihydropyridines : Diltiazime, and Verapamil

Doses: Nifedipine: 30 – 90 mg PO daily

Amlodipine: 2.5 -10 mg PO daily

Side effects : *Dihydropyridines:* headache , tachycardia , GI disturbance

Non dihydropyridines have cardio depressant effect and their use may be problematic in CHF patients

Contraindication: Heart block, heart failure

F. ***ACE inhibitors:*** inhibit the conversion of angiotensin I to angiotensin II (a potent vasoconstrictor). By doing so ACE inhibitors reduce peripheral resistance. In addition they reduce aldosteron production, reducing the retention of sodium and water. ***Captopril , Nezapril , Enalapril , Fosinopril , Ramipril***

Doses: ***Captopri*** : 12.5 -75 mg PO BID

Enalapril: 2.5-40 mg daily

Side effects: Cough, Leucopenia, angioedema, hyperkalemia.

Contraindicated in: Bilateral renal artery stenosis, Renal failure.

G. ***Angiotensin receptor blockers***: they block the angiotensin system without causing some of the annoying side effects of ACE inhibitors such as cough.

Losartan: 25-50 mg once or twice daily

Side effects: hypotension

Stepwise prescription of anti-hypertensive medication:

- Diuretics are often preferred as first line drugs. They may be effective alone in mild hypertension. However most of the time they are used in combination with other drugs like: β –blockers, ACE inhibitors or Calcium channel blockers. The addition of 12.5 – 25 mg of Hydrochlorothiazide will potentiate the activity of a number of antihypertensive drugs, particularly ACE inhibitors. Such combination has an additive effect, controlling blood pressure in up to 85% of patients
- The dosage of be anti-hypertnsivedrugs should be escalated till BP is well controlled
- If one drug fails to control the BP consider changing the antihypertensive drug
- If the blood pressure is still uncontrolled consider using multiple drugs which act at different sites and have additive effect. Most drug combinations, using agents that act by different mechanisms, have an additive effect. The combination of a calcium channel blocker with either an ACE inhibitor or a dihydropyridine calcium channel blocker and a beta-blocker has additive effects.
- Some combinations may not be additive, including a beta-blocker and ACE inhibitor, a beta-blocker and an alpha1-blocker and an alpha2 stimulant.
- Some combinations may have additive adverse effects; these include a beta-blocker combined with Verapamil or Diltiazem, which leads to cardiac depression, bradycardia, or heart block.
- If the BP is still resistant to treatment add direct vasodilators.

Choice of anti hypertensive drugs in certain situations for which a specific class of drug may be administered.

- ***Thiazides (e.g.Hydrochlorothiazide)***:is the preferred therapy for uncomplicated hypertension , systolic hypertension in elderly people and older diabetic patients without nephropathy
- ***ACE inhibitor:*** should be the initial treatment in situations in which hypertension is associated with congestive heart failure, diabetes mellitus with proteinuria, and post myocardial infarction with systolic left ventricular dysfunction. In patients who develop persistent cough while on ACE inhibitor therapy, an angiotensin II receptor antagonist may be substituted, but these agents' efficacy in lowering cardiovascular mortality rates has not yet been proven.
- ***B-blockers***: are often preferred in post–myocardial infarctionand useful also for uncomplicated hypertension.
- ***A diuretic or a long-acting calcium channel blocker*** may be more effective in elderly patients with isolated systolic hypertension.
- ***Calcium channel blockers:*** Nifedipine is preferred therapy for systolic hypertension and an alternative therapy in uncomplicated hypertension.
- ***Central acting agents*** (e.g. Methyldopa) may be used as alternative therapy for uncomplicated hypertension.

Hypertensive crisis: is defined as severe hypertension characterized by diastolic blood pressure greater than 130 mmHg. Blood pressure elevation to such degree can cause vascular damage, encephalopathy, retinal hemorrhage, renal damage and death. 1 –2% of the hypertensive population develop this complication. It is categorized into two:

- ***Hypertensive Emergency*** in which there is acute impairment of an organ system (CNS, CVS, Renal). In these conditions, the blood pressure should be lowered aggressively over minutes to hours.
- ***Hypertensive Urgency*** in which BP is high and there is potential risk but not yet caused acute end-organ damage. These patients require BP control over several days to weeks.

Diagnosis: A diastolic pressure of 130 mmHg, funduscopic finding of papilledema, change in neurologic and mental status and abnormal renal sediments are the hallmarks of hypertensive crisis

Approach to patients with hypertensive crisis:

- Rapid assessment of the patient with brief history and targeted physical examination (of the CNS, CVS , retina),
- ***Laboratory investigations*** :
    - CBC
    - Urinalysis
    - Renal function test
    - ECG

Treatment "treats the patient, not the number"

General measures:

Initial considerations: look if the patient is in a stressful situation .Place the patient in a quiet room and reevaluate after initial interview, some patient's BP lowers below a critical level after relaxation.

Pharmacologic treatment:

- If the patient has Hypertensive emergency, lower the BP rapidly by 25% of the diastolic BP and not less than 95mmHg.
- Use rapidly acting antihypertensive (IV hydrallazine, Soduim Niteroprusside or Sublingual Nifedipine).
    - ***Soduim Niteroprusside***: is an effective treatment.
        - **Dose** : 0.5-8 microgram/kg/min through continuous IV infusion till BP is lowered to the desired level
    - ***Hydralazine*** 10 -20 mg IV stat to be repeated every 20 -30 minutes can also be used
    - ***Labetalol*** : 2mg /min through continuous IV infusion
- As the patient's BP stabilizes start long term oral anti hypertensive agents.
- Those patient with urgency, could be discharge with close follow –up and oral medication.

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Hypertensive vascular diseases, pages 1463-1480

2. Myers R. Allen , National Medical Series for independent Study (NMS) 3rd edition Medicine, Hypertension, 346-364.

8. Pericarditis and Pericardial effusion

Learning objectives: *at the end of this lesson the student will be able to:*

1. *Define Pericarditis.*
2. *List the etiologies of Pericarditis.*
3. *Describe the different types of Pericarditis.*
4. *Understand the pathophysiology of Pericarditis.*
5. *Identify the clinical manifestation of Pericarditis.*
6. *Identity* acute and *chronic complications of Pericarditis.*
7. *Understand the diagnostic approach of Pericarditis.*
8. *Understand the principle of management of Pericarditis.*

Definition: Pericarditis is an inflammation of the pericardium surrounding the heart. Percarditis and cardiac tamponade are clinical problems involving the potential space surrounding the heart or pericardium. Pericarditis is one cause of fluid accumulation in this potential space and cardiac tamponade is the hemodynamic result of fluid accumulation.

Pathophysiology: The pericardium consists of an outer fibrous layer (parietal pericardium) and an inner serous layer (visceral pericardium). Normally the two layers are separated by a small quantity of fluid (15-50 ml).The pericardium serves as a protective barrier from the spread of infection or inflammation from adjacent structures. It also prevents sudden dilatation of the cardiac chambers during exercise and hypervolumia. It restricts the anatomic position of the heart and minimizes friction with the surrounding structures.

Approximately 120 cc of additional fluid can accumulate in the pericardium without an increase in pressure. Further fluid accumulation can result in marked increases in pericardial pressure, eliciting decreased cardiac output and hypotension (cardiac tamponade). The rapidity of fluid accumulation influences the hemodynamic effect.

Table –III-8-1. Classification of Pericarditis

Clinical classification	***Etiologic Classification***
I. ***Acute pericarditis (<6 weeks)***	***I. Infectious Pericarditis***
a. Fibrinous	a. Viral
b. Effusive (serous or sanguineous)	b. Pyogenic
II. ***Subacute pericarditis (6 weeks to 6 months)***	c. Tuberculous
	d. Fungal
a. Effusive-constrictive	***II. Noninfectious Pericarditis***
b. Constrictive	a. Uremia
III. ***Chronic pericarditis (over 6 months)***	b. Acute myocardial infraction
	c. Neoplasm
a. Constrictive	d. Idiopathic
b. Effusive	***III. Hypersensitivity/autoimmune***
c. Adhesive (nonconstrictive)	a. Rheumatic fever
	b. Rheumatoid arthritis
	c. SLE
	d. Posttraumatic

TB pericarditis is quite common in HIV positive patients.

Clinical features

Pericarditis

- The most common symptom of acute pericarditis is precordial or retrosternal chest pain, usually described as sharp or stabbing.
    - Pain may be of sudden or gradual onset and may radiate to the back (left trapezial ridge), neck, left shoulder, or arm.
    - Movement or inspiration may aggravate the pain.
    - Pain may be most severe when the patient is supine and can be relieved when the patient leans forward while sitting.
- Commonly associated symptoms include low-grade intermittent fever, dyspnea, cough, and dysphagia.

- In tuberculosis pericarditis, fever, night sweats, and weight loss are commonly noted (80%).
- Some patients may present with acute abdominal pain.

Cardiac tamponade

- Patients may present subacutely with symptoms of anxiety, dyspnea, orthopnea, fatigue, or altered mental status.
- Patients may have a history of medical illnesses associated with pericardial involvement, particularly end-stage renal disease (ESRD).
- Traumatic tamponade may present with acute dyspnea or altered mental status.
- A waxing and waning clinical picture may be present in intermittently decompressing tamponade.

Physical findings:

Pericarditis

- The classic sign of acute pericarditis is ***pericardial friction rub***, which is scratchy, leathery sound heard during both systole and diastole. It is best, heard at the lower left sternal border or apex when the patient is positioned sitting forward. Friction rub may be transient from one hour to the next and is present in approximately 50% of cases. A friction rub may be distinguished from a cardiac murmur by its changing character from heartbeat to heartbeat and patient position changes. A friction rub is closer to the ear on auscultation than a murmur.
- Fever: usually is low grade, but it may occasionally reach 39^0 C.
- Cardiac arrhythmias: Premature atrial and ventricular contractions occasionally are present.
- Tachypnea and dyspnea: Dyspnea is a frequent complaint and it may be severe with myocarditis, pericarditis, and tamponade.
- ***Ewart sign*** (dullness and bronchial breathing between the tip of the left scapula and the vertebral column)
- Hepatomegally and ascites may be found.

Cardiac tamponade

- As the volume of pericardial fluid increases, the capacity of the atria and ventricles to fill is mechanically compromised, leading to reduced stroke volume and tamponade. It is influenced by volume and rate of accumulation.

- ***Beck triad*** (jugular venous distention, hypotension, and muffled heart sounds)
- Neck vein distension is a common finding: but Kussmaul's sign is absent
- ***Hypotension to the extent of shock:*** may occur when the cardiac stroke volume is significantly reduced and tissue perfusion is compromised
- ***Pulsus paradoxus***: abnormal fall in blood pressure by more than 10 mm Hg during inspiration.
- ***Narrow pulse pressure***: indicates reduced left ventricular stroke volume.
- ***Cyanosis***
- ***Varying degrees of altered consciousness***

Diagnostic workup

Laboratory studies:

- CBC with differential
- Elevated erythrocyte sedimentation rate (ESR)
- HIV testing
- Antinuclear antibody, rheumatoid factor

Imaging Studies:

- ***Chest radiography:*** A bottle–shaped heart can be seen with excessive pericardial fluid accumulation. In cardiac tamponade (or large effusions), the chest x-ray may demonstrate an enlarged cardiac silhouette after 200-250 ml of fluid accumulation. This occurs in patients with slow fluid accumulation, compared to a normal cardiac silhouette seen in patients with rapid accumulation and tamponade. Thus, the chronicity of the effusion may be suggested by the presence of a huge cardiac silhouette.
- ***ECHO:*** minimal pericardial effusion in pericarditis and significant pericardial effusion in Chonic pericarditis or Cardiac tamponade.
- ***ECG :***
  - ***Acute pericarditis:*** diffuse ST segment elevation without reciprocal ST segment depression and depression of PR segment is unique to acute pericarditis reported in up to 80% of viral pericarditis cases..
  - ***Cardiac tamponade or massive effusion***: electrical alternans is pathognomonic of cardiac tamponade and is characterized by alternating levels of ECG voltage of the P wave, QRS complex, and T waves. This is a result of the heart swinging in a large effusion. Low voltage of ECG.

Treatment

1. ***Acute Pericarditis***:

Treating pain and inflammation:

- Nonsteroidal anti-inflammatory drugs (NSAID): ASA, Indomethacine and Ibuprofen are effective in reducing the inflammation and reliving the chest pain.
- Steroid therapy: intractable cases of pericarditis that fail to respond to NSAID.

Specific therapy: should be directed towards the cause of pericarditis.

E.g. Patients with TB pericarditis should be treated with ant TB along with steroid

2. Cardiac tamponade

- Patients with evidence of cardiac tamponade need emergency pericadiocentesis i.e. removal of fluid from pericardial sac.

Complications of Pericarditis:

- Recurrence : pericarditis may recur in 15-32% of patients
- Cardiac tamponade
- Chronic constrictive pericarditis
- Cardiac perforation at time of pericardiocentesis
- Bronchopericardial fistula: This was noted as a complication of multi–drug-resistant TB in a patient with HIV.

Prognosis: The prognosis of pericarditis depends upon the etiology of the pericardial infection or inflammation as well as the presence of a pericardial effusion and/or tamponade.

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Pericardial disease, pages 1414-1419.

9. Ischemic Heart Diseases

Learning objectives: *at the end of this lesson the student will be able to:*

1. *Define Ischemic Heart Diseases.*
2. *List the etiologies of Ischemic Heart Diseases.*
3. *Describe the different types of Ischemic Heart Diseases.*
4. *Understand the epidemiology of Ischemic Heart Diseases.*
5. *Understand the pathophysiology of Ischemic Heart Diseases.*
6. *Identify the clinical manifestation of Ischemic Heart Diseases.*
7. *Identity consequences of Ischemic Heart Diseases hypertension.*
8. *Outline the diagnostic approach of Ischemic Heart Diseases.*
9. *Understand the principles of management of Ischemic Heart Diseases.*
10. *Refer patients with Ischemic Heart Diseases to better facility.*

Background

Ischemic Heart Diseases manifests due to an imbalance in myocardial oxygen supply and demand, that results in myocardial hypoxemia. The most common cause of myocardischemia is atherosclerotic disease of the coronary arteries.

Epidemiology

- IHD is the leading cause of morbidity and mortality in developed countries and it incurs greater economic cost.
- The prevalence of IHD is also on the rise in developing countries as there is a change in the life style associated with urbanization including sedentary life style, smoking, obesity high fat and energy diet and the associated increased prevalence in Diabetes mellitus.
- Larger increases in prevalence of IHD through out the world are projected, and the it is likely to become the most common cause of death worldwide by 2020

Etiology/Pathophysiology

Myocardial ischemia reflects an imbalance between myocardial oxygen supply and demand. Myocardial oxygen demand is mainly determined by heart rate, the force of ventricular contraction, and ventricular wall tension, which is proportional to the ventricular

volume and pressure. Unless there is a proportionate rise in oxygen supply, conditions that increase oxygen demand such as physical exertion result in ischemia
Atherosclerosis of coronary artery (CAD) is the most common cause IHD.

Risk factors for Coronary artery disease / Ischemic heart diseases

- ***Age***: the risk of CAD increases progressively with age. The risk of death from CAD is 1.5 in 1000 individuals at age 50.
- ***Gender*** : IHD is more prevalent in men than in women >The difference is more marked in premenopausal women compared to men of similar age
- ***Lipid abnormalities*** : increased serum LDL level and reduced HDL level with hypertrigyceridemia favors the deposition of lipds and choletrol in atherosclerotic plaques
- ***Smoking*** : cigarette smokers are 60% more likely to develop CAD than non smokers
- ***Hypertension***: increases the risk of CAD both in men and women.
- ***Diabetes mellitus*** : is associated with significant increase in the risk of CAD
- ***Family history***: a familial predisposition to CAD exists
- ***Oral contraceptive pills***: use of OCP is associated with increased risk of CAD.
- ***Other risk factors***: Gout, Obesity.

Atherosclerosis is focal narrowing of arteries which results from a plaque formation. In CAD, atherosclerosis risk factors such as hyperlipidemia, cigarette smoking, diabetes mellitus, and hypertension apparently disrupt the normal functioning of the vascular endothelium. Plaques are formed as a result of

- Intimal smooth muscle proliferation probably as a result of endothelial damage
- Lipids (Cholesterol esters) are deposited at the center of plaques and also with in smooth muscle cells
- A fibrous cup made of connective tissue covers the plaque

As the stenotic lesions grow, perfusion pressure distal to the lesions decreases; in response, coronary arterioles dilate to maintain adequate blood flow preventing ischemic symptoms at rest. During exertion the myocardial oxygen demand increases which couldn't be matched by

the perfusion via the narrowed coronary artery. The resulting myocardial ischemia results in chest pain, called angina pectoris, which is relived by taking rest.

Sometimes atherosclerotic plaques may rapture and a fibrin thrombus is formed overe the plaque which completely blocks the narrowed coronary artery and result in myocardial infarction.

Clinical features of Coronary artery diseases.

1. ***Angina pectoris*****:** *is a chest pain or pressure produced by myocardial ischemia.*
   - Anginal pain is often precipitated by exertion. Other factors that increase myocardial oxygen demand (e.g. emotional stress, eating meal, sexual intercourse) may also precipitate angina.
   - The chest pain in angina is squeezing in type or a feeling of pressure or tightness in the chest. Sometimes it can be burning in nature or felt as epigatric discomfort.
   - Radiation: the pain radiates to the left shoulder, left jaw, teeth or to the left arm. Sometimes it may radiate to the right arm.
   - The pain in angina is often reproducible with the same degree of physical exertion. The symptom usually begins with low intensity, increase over 2-3 minutes and often lasts less than 15 minutes. Episodes lasting morethan30 minutes suggest myocardial infarction may have occurred

Types of Angina

A. ***Chromic stable angina***: angina which recurs under similar circumstances and with similar frequency over time.
B. ***Silent ischemia***: for every episode of symptomatic ischemia that the patient suffers, there are usually four to five episodes of silent (asymptomatic) ischemia. This episode can be detected by ECG including stress ECG. Such episodes are less severe in nature and shorter in duration.
C. ***Unstable angina***: is a term applied to angina when a change in status occurs. *Unstable angina is progressive and it may be ominous feature of imminent myocardial infarction. So physicians and patients should be aware that close observation and intensive therapy are required. It represents a more serious situation tan chronic stable angina.*
   i. ***New onset angina*** is an angina that progresses in severity , duration or frequency over 1-or 2 months

ii. ***Resting angina***: is particularly worrisome because it implies decreased supply, rather that increased demand, is causing angina. This suggests possible occlusion is imminent.

C. ***Varian (Prinzmetal's) angina*** *:*

- This is a type of angina resulting from transient coronary spasm, which usually but not always associated with fixed atherosclerotic lesion. The spasm produces total but transient coronary occlusion.
- It usually occurs at rest (often at night) and episodes are frequently complicated with ventricular arrhythmias.

History

- In a patient presenting with a history of recurrent chest pain, obtain a detailed symptom history, including onset, quality, location, duration, radiation, and precipitating and relieving factors.
- Determine the presence or absence of each of the three following symptom complex characteristics:
  1. Substernal discomfort with a characteristic quality and duration
  2. Symptoms provoked by exertion or emotional stress, and
  3. Symptoms relieved by rest or nitroglycerin.
- Based on the number of symptom complex present, angina can be classified as :
  - ***Typical (definite)*** angina if all three of the characteristics are present
  - ***Atypical angina (probable)*** if two of the characteristics are present or
  - ***Non-cardiac chest pain*** if none or one of the characteristics is present.
- If the patient's symptoms are consistent with typical angina, sub-classify the angina as stable (unchanged for 2 or more months) or unstable (rest, new-onset, or increasing) angina.
- In patients with typical (definite) or atypical (probable) angina, ask about functional limitations
- Ask about any episodes of dyspnea, palpitations, or dizziness with or without chest pain. If the patient has experienced any such episodes, ask about the same symptom variables that are applicable to typical angina
- Assess potential risk factors for CAD, including those related to lifestyle, habits, past medical history, family history, and hormone therapy

- Ask about a history of symptoms, such as exertional dyspnea, orthopnea, and bilateral leg swelling, that suggest left ventricular (LV) dysfunction or heart failure and nocturia
- Ask about other potential causes of chest pain, especially if the symptoms have changed, new symptoms have arisen, or the patient is at low risk for CAD.

Physical Examination

- In a patient presenting with suspected stable angina, perform a complete physical examination to help identify the cause of the chest pain and any comorbid disorder(s)
- Assess the vital signs, especially for hypertension, tachycardia, bradycardia, arrhythmia, and tachypnea
- Closely examine the head and neck, especially for signs of anemia (mucous membrane pallor), thyroid disease (exophthalmos, thyromegaly), hypercholesterolemia (Xanthelema which is the deposit of lipids in the skin of the eyelids) or atherosclerosis (carotid bruit)
- Perform a general and peripheral vascular examination to identify signs of generalized or peripheral atherosclerosis (e.g., inequality of blood pressure in arms, diminished pedal pulse, and abdominal aneurysm).
- Carefully examine the heart for evidence of hypertrophy, murmurs, and third or fourth heart sounds (S3, S4).
- Examine the lungs for rales (crackles) and other abnormal breath sounds.
- Examine the lower extremities for dependent (ankle) edema, tendinous xanthomas (lipid deposit), weak pulses, or cutaneous signs of ischemia or necrosis.

Diagnostic workup:

Electrocardiography:

Resting ECG:

- ECG taken when the patient is not in pain may be normal. The presence of new horizontal or down sloping of ST segment depression and new T-wave inversion are suggestive of myocardial ischemia.
- ST segment elevation associated with pain which returns to normal as the pain wanes suggest variant angina

Stress ECG:

- Recording ECG during exercise increases the sensitivity and specificity of ECG. This helps to quantify the patient's exercise tolerance. The presence of new horizontal or down sloping of ST segment depression has sensitivity of 70 % and specificity of 90 %.

Radiologic/Imaging

- Chest-ray in patients with symptoms and signs of congestive heart failure
- Stress radionuclide ventricuography
- Stress echocardiography
- Cardiac catheterization

Other laboratory tests

- Hemoglobin or CBC, fasting blood glucose,
- Serum lipid profile

Differential Diagnosis

Consider other cause of chest pain like

- Pleurisy
- Pneumonia
- Pericarditis
- Ischemia associated with aortic stenosis, or hypertrophic cardiomyopathy

Treatment for Angina

Therapy for angina should be directed either towards reducing myocardial oxygen demand, or to compensate for impaired flow through diseased coronary arteries or at increasing myocardial oxygen supply (i.e. blood flow)

General measures

Lifestyle Measures

- Counsel patients about cessation of smoking
- Diet ('healthy' diet like low fat and low caloric diet with increased habit of eating fruits and vegetables)
- Regular exercise
- Weight reduction.

Medical therapy

a) Nitrates: this class of drugs produce venodilation and to lesser extent arteriolar dilation. These effects reduce blood pressure and reduce cardiac size.

Instruct patients about how and when to use short-acting nitrates (e.g., 0.4 mg sublingual nitroglycerin) for acute attacks, unless nitrates are contraindicated Consider long-acting nitrates in patients who have refractory chest pain despite maximal tolerated beta-blocker therapy, or in patients who would benefit from after load reduction

To avoid nitrate tolerance in patients requiring long-acting nitrates, prescribe a 10- to 12-hour nitrate-free period daily.

Nitroglycerine 0.3-0.6 mg sublingual as soon as the pain starts or 5 minutes before a stressful activity.

Isosorbide dinitrate slow release: 10-60 mg PO TID or 2.5 -10 mg sublingual every 4-6 hrs

b) β-blockers: reduce heart rate and myocardial contractility. By doing so reduce cardiac oxygen demand. Propranolol, Atenolol, Nadolol, and Timolol may be used.

Propranolol: 20 -80 mg PO BID to QID

Metoprolol: 25-200 mg Po BID

Atenolol: 50 -150 mg PO daily

N.B. Consider the patient's concomitant health problems, when selecting a specific beta-blocker

Contraindicated in patients with asthma and severe form of CHF

c) Calcium channel blockers: decrease the tone of the smooth muscle of coronary arteries.

These drugs are especially effective in preventing coronary spasm that cause variant angina.

Nifedipine XL: 30 mg PO O daily

Verapamil: 180-240 mg daily

Amlodipine: 5-10 mg daily

- Consider calcium channel blockers when beta-blockers are contraindicated or are not tolerated.

- Consider using combination therapy cautiously (e.g., a beta-blocker and calcium antagonist or nitrate) for patients who fail to respond adequately to monotherapy.

d) Anti-platelet agents :

Aspirin: small dose of aspirin is recommended for patients with angina to prevent the occurrence of myocardial infarction.

Dose: 75 – 150 mg PO daily.

e) Lipid lowering drugs :Generally, prescribe a lipid-lowering medication (statins) and a low-fat, low-cholesterol diet for patients with CAD and elevated low-density lipoprotein (LDL) levels to achieve an LDL level of less than 100 mg/dl

f) ACE inhibitor : may be beneficial in all patients with significant CAD by angiography or in those with previous MI who also have diabetes and/or LV systolic dysfunction

g) Treat comorbidities that can provoke or exacerbate angina (e.g., hypertension, diabetes mellitus, hyperthyroidism, pulmonary disorders, anemia)

- **N.B Acute Care/Hospitalization**: Always refer patients presenting with new-onset, rest, or increasing angina to an emergency department, and hospitalize a patient with clinical evidence of unstable angina or myocardial infarction.

Surgical interventions:

- Percutanous transluminal coronary angioplasty
- Artherectomey
- Coronary artery bypass surgery

Complications

- In patients with chronic stable angina, be sensitive particularly to accelerating symptoms, indicating development of unstable angina.

Prognosis

The main prognostic indicators in patients with ischemic heart disease (IHD) are:

- The status of left ventricular (LV) function
- The location and severity of coronary artery narrowing
- The severity or activity of myocardial ischemia
- The presence of complex arrhythmias

Acute Myocardial Infarction (AMI)

AMI develops when the myocardium is deprived of its blood supply (Oxygen) for a significant amount of time.

AMI may be classified in to

- ***Transmural myocardial infarction*** : results from obstruction of coronary arteries by thrombus or coronary spasm
- ***Non Transmural (subendocardial) myocardial infarction*** the cause of which remains uncertain

Symptoms:

- ***Chest pain***: Sever squeezing or crushing type of chest pain that lasts for more than 30 minutes and not relived by rest or sublingual nitroglycerine. The pain radiates in a similar pattern to angina. The pain usually occurs when the patient is a rest or involved in minimal activity. Emotional stress may also precipitate AMI.

- ***Other associated symptoms***; Nausea, vomiting, diaphoresis and shortness of breath, anxiety and sense of impending doom.

Physical examination

- The patient is in pain and quite apprehensive often appears ashen
- Hypotension and tachycardia may be present if the infarction is extensive
- There also may be signs of CHF (E.g. elevation of JVP , pulmonary rales , and S_3 gallop)
- A new murmur of mitral regurgitation may be present.

Complications of AMI

Arrhythmias:

- Lethal ventricular arrhythmias are the commonest cause of death in the first hour. This may include ventricular tachycardias and ventricular fibrillation
- Atrial arrhythmias ; atrial fibrillation and atrial flutter

Acute conduction system abnormality

- The conduction system may be part of the myocardium affected during infarction. This may lead to bradycardia and heart block
- Inferior wall MI occurs when the right coronary artery is occluded. Since it supplies the AV node, Sinus bradycardia and varying degree of AV block occur during inferior myocardial infarction.

- Anterior myocardial infarction may lead to Right or left bundle branch blocks

Pump failure

- ***Congestive heart failure*** is most likely to occur, when 30 % of the myocardium is infracted ,
- ***Cardiogenic shock***, defined as Systolic BP < 90 mmHg: occurs if more than 40% of the myocardium is affected by infarction.

Mitral regurgitation: may occur if the papillary muscles are affected by infarction.

Ventricular septal defect:

- The left ventricular septum may become infracted either in anterior or inferior AMI. , leading to rapture of the septum.

Cardiac rapture:

- Myocardial infarction of the free wall may lead to eventual perforation of the heart. This complication, which results overwhelmingly cardiac tamponade, is nearly always fatal.

Left ventricular aneurysm:

- The infracted myocardium may evaginate and heal with fibrous connective tissue. It may be a source for cardiac emboli.

Pericarditis: post AMI pericarditis (Dressler's Syndrome) which is believed to be autoimmune in origin.

Diagnostic work up

1. ***ECG:*** is diagnostic in approximately 85% of cases.
    - **Transmural MI/Q-wave MI** : ST segment elevation in those leads reflecting the area of myocardial infarction ,As ST segments fall , Q waves appear and T waves become inverted
    - **Subendocadial infarction/Non Q wave MI**; ECG findings are less certain and ST segment depression may be the only finding
2. ***Cardiac enzymes*** : as myocardial necrosis occurs , the myocardium releases cardiac enzymes
    - Creatine phospho kinase (CPK) elevation appears 6 hours after infarction
    - Aspartate aminotransfarase (AAST or SGOT) elevates 12 hrs after infarction
    - Lactate dehydrogenase (LDH): starts to elevate 24 hrs after infarction.

- Cardiac specific troponin-T and cardiac specific troponin- I, are also elevated and they are very specific to cardiac muscles. (So this is the preferred biomedical test in Developed countries.). These proteins are not normally detectable in the blood of healthy individuals , but rise > 20 X in patients with AMI.

3. Cardiac Imaging

- Echo: Decrease myocardial function (decrease ejection fraction) and significant wall motion abnormality may be detected
- Radionuclide imaging techniques

Management of patients with acute myocardial infarction

Management of AMI is beyond your capacity and immediate referral to hospitals with intensive care unit (ICU) facility is mandatory. However, the management of acute MI is outlined as follows

A. *Emergency management* :Management of patients should start before they reach the hospital emergency room

1. General measures

- Reassure and make the patient comfortable
- Supply O_2 by mask
- Secure IV line
- Give Aspirin 160-325 mg tablets –helps to prevent further platelet aggregation

2. Treatment of pain:

- ***Nitroglycerin***: sublingual up to three doses of 0.4 mg should be administered at about 5 minutes interval for up to three doses.
- ***Morphine sulphate:*** is very effective analgesic for pain associated with AMI origin .It is administered in small doses of 2-4 mg IV every 5 minutes

3. Limitation of infarct size through reperfusion or revascularization.:

- ***Thrombolysis/Fibrinolysis***
  - Thrombolytic agents : such as Streptokinase , t-plaminogen activator, urokinase : these drugs are given to dissolve the occlusive thrombus and promote reperfusion of the infarct related artery reduces

mortality from myocardial infarction when administered within 6 hours of the onset of chest pain.

Contraindication: History of Cerebrovascular hemorrhage, marked hypertension, bleeding disorder.

- ***Direct percutanous transluminal coronary angioplasty:*** in best facilities in the developed countries this is the preferred method to restore perfusion of occluded coronary artery. When performed by experienced physicians the short and long term outcomes are much better than what can be archived through thrombolysis or fibrinolysis.

B. ***Hospital phase management:*** patients should be referred and admitted to coronary artery units or ICU.

1. General measures

- ***Activity :*** absolute bed rest for the first 12 hours , Sitting on their bed in the first 24 hours , the patient may ambulate in their rooms by the 2nd or 3rd day
- ***Diet :*** Because of the risk of emesis and aspiration soon after AMI , patients should receive either nothing or only clear liquids by mouth for the first 4-12 hrs. The diet should be low fat low calori and rich in Potassium
- ***Bowel motion***: constipation is common and straining may precipitate AMI . Fibrous diet and Stool softeners like bisacodyl or Dioctyl sodium sulfosuccinate 200 mg /day are recommended. If the patient remains constipated laxatives can be prescribed.
- ***Sedation:*** many patients require sedation during hospitalization to withstand the period of enforced inactivity with tranquility.
    - Diazepam15 – 30 mg or Lorazeam 0.5 to 2mg given 3-4 X daily.

2. Pharmacological therapy

a) Antithombotic agents and anti platelet agents :

- Unfractionated heparin : may be given in patients where there is a risk of cardiac thrombus formation and subsequent emboli
- Anti platelet agents : ASA 75-150 mg Po daily to prevent recurrence of AMI

b) ***β-Blockers***: have short term and long term benefits for patients with AMI.

- The short term benefit is they relive pain and decrees the risk of malignant arrhythmias

- Long term benefits are : improved myocardial performance and facilitate the healing process in Post myocardial infarction patients

  Metoprolol: 25-200 mg BID

  Atenolol: 50-150 mg Po daily

Contraindication: Severe CHF, AV block

c) ***ACE inhibitors*** ; reduce the mortality rate and improve long term survival in post AMI patients by preventing cardiac remodeling which may have lead to progressive heart failure. Their effect is additive to what is archived with Aspirin and β-blockers. . The maximum benefit is seen in high risk patients (elderly patients , significant LV dysfunction) . ACE inhibitors should be prescribed within 24 hours and maximum benefit is archived when they are given at higher doses that are recommended. In patients with CHF ACE inhibitors are given indefinitely.

Captopril: Start with smaller dose 12.5 mg PO day to gradually escalate to 75 mg Po BID

Enalapril: Start with 2.5 mg PO daily and escalate gradually to 40 mg Po daily

Management of Complications

Malignant arrhythmias;

- Cardiac defibrillation
- Prophylactic lidocaine
- Other antiarrhythmic agent; bertyluim tosylate and procainamide

Treatment of serous conduction disturbances;

- Sinus bradycardia :Atropine 2mg IV may restore conduction and restore heart rate
- AV block : Trans cutanous cardiac pace makers

Heart failure:

- Diuretics, Salt restriction, ACE inhibitors, vasodilators. Use of digoxin is controversial.

Cardiogenic shock: do Echocardiography to assess the ventricular function

- IV infusion of fluids to maximize left ventricular filling
- Use of vasopressors: Dubutamine, dopamine) in IV infusion.
- Intraaortic balloon pumping
- Percutanous transluminal angioplasty

Prognosis: depends on two factors

The extent of coronary artery disease in terms of the number of vessels affected

- Patents with uncorrected main left coronary artery disease have approximately a 20 % mortality in the first year
- Single vessel coronary artery has 2 % annual mortality.
- Double vessel disease: have approximately a 2- 4 % annual mortality.
- Triple vessel disease: have 5-8 % annual mortality.

The extent of ventricular damage: left ventricular ejection fraction

- An ejection fraction of <40 % doubles the yearly mortality rate at each level of extent of coronary disease.

Revascularization: significantly improves the short term and long term morbidity and, mortality when it is done at the right time by an expert hand.

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Ischemic heart disease, pages 1434-1448.

2. Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Ischemic heart disease, pages 15-28.

10. Cardiac Arrhythmias

Learning objectives: *at the end of this lesson the student will be able to:*

1. *Define Cardiac arrhythmias*
2. *List the etiologies of arrhythmias.*
3. *Classify the different types of arrhythmias.*
4. *Understand the pathophysiology of arrhythmias.*
5. *Identify the clinical manifestation of arrhythmias.*
6. *Identity consequences of arrhythmias.*
7. *Understand the diagnostic approach arrhythmias.*
8. *Understand the principle of management of arrhythmias.*
9. *Refer patients with arrhythmias to appropriate centers*

Definition: Cardiac arrhythmias are changes in the regular beating of the heart. The heart may seem to skip a beat or beat irregularly or beat very fast or very slow.

***The normal heart beat of a person ranges from 60* -100 beats/min.**

- Many arrhythmias occur in people who do not have underlying heart disease.
- Most of the time, there may not be a recognizable cause of an arrhythmia.
- Heart disease may cause arrhythmias. Other causes include: stress, caffeine, tobacco, alcohol, diet pills,"Khat", cough and cold medicines.
- In some people, arrhythmias are associated with heart disease. In these cases, heart disease, not the arrhythmia, poses the greatest risk to the patient.
- In a very small number of people with serious symptoms, arrhythmias themselves are dangerous. These arrhythmias require medical treatment to keep the heartbeat regular.
- Arrhythmias occur commonly in middle-age adults. As people get older, they are more likely to experience an arrhythmia.
- Patients with arrhythmias often complain that they felt their heart beat very fast, experienced a fluttering in their chest, or noticed that their heart skipped a beat. Almost everyone has also felt dizzy, faint, or out of breathe or had chest pains at one time or another.

Classification of Arrhythmias

1. ***Bradyarrhythmias:*** are arrhythmias in which the heart beats slower than normal. They result from inadequate sinus impulse production or from blocked impulse propagation. They are not usually cause of concern unless the patient develops syncope or presyncope.
    - Sinus bradycardia
    - Sinus pause
    - AV block
2. ***Tachyarrythmias***: are arrhythmias in which the heart beats faster than normal.

    A. Atrial tachyarrhythmias: tachyarrhythmias originating from the atria.

    i) Regular atrial tachycardias : the heart beats faster but the rhythm is regular
        - Sinus tachycardia
        - Paroxysmal atrial tachycardias
        - Atrial flutter with constant conduction

    ii) Irregular atrial tachycardias : the heart beats faster and the rhythm is irregular
        - Atrial fibrillation
        - Multifocal atrial tachycardia
        - Atrial flutter with irregular conduction

    B. Ventricular Tachyarrhythmias: tachyarrhythmias originating from the ventricles.
        - Premature ventricular contraction
        - Ventricular tachycardia
        - Ventricular fibrillation

Bradyarrhythmias

1. ***Sinus bradycardia:***

Causes

- Physical conditioning in professional athletes
- Hypothyroidism
- Sinus node dysfunction

Therapy

- If it is physiologic no need for treatment
- If it is due to sinus dysfunction and severe (the HR is < 35 beats/min) :

- Atropine : 1mg IV may temporarily increase the sinus rate
- Cardiac Pacemaker implantation.

2. ***Sick sinus syndrome:*** The sinus node does not fire its signals properly, so that the heart rate slows down. Sometimes the rate changes back and forth between a slow (bradycardia) and fast (tachycardia) rate
3. ***AV blocks:*** all of the impulses generated from the sinus node are not conducted to the ventricles

2nd degree AV block: Some atrial impulses are blocked and not transmitted to the ventricles

- **Mobitz Type I (Wenckebach) block**: the PR interval is progressively prolonged until a generated P wave is not conducted.
- **Mobitz Type II block:** there is no prolongation of the PR interval before the dropped beat. Often conduction is in a ration of 2: 1and it is prolonged enough to cause symptomatic bradycardia.

3rd Degree (Complete) heart block: No atrial impulses are conducted and the atria and the ventricles are contracting independently. The heart rate drops significantly to a range of 20- 40 beats/min and patients become symptomatic.

Therapy:

- **Pharmacologic therapy**: reserved only for acute situations to temporarily increase the ventricular rate.
  - Atropine 0.5-2 mg IV or Isoproterenol 1-4 microgram/min IV
- ***Permanent cardiac pacemakers*** : most symptomatic AV blocks need permanent pacing

Sinus tachycardia: the sinus node sends out electrical signals faster than usual, speeding up the heart rate. It represents physiologic or pathologic increase in the sinus rate ≥100 beats/min. It rarely exceeds > 200 beats/min

Supraventricular tachycardia (SVT), paroxysmal atrial tachycardia (PAT). A series of early beats in the atria speed up the heart rate (the number of times a heart beats per minute). In paroxysmal tachycardia, repeated periods of very fast heartbeats begin and end suddenly. These arrhythmias are sudden onset, often occurring in patients with otherwise normal heart, and characterized by a heart rate of 150-250 beats /min

Common causes

- Exercise , fever
- Anxiety ,thyrotoxicosis
- Hyopoxemia ,hypotension
- Heart Failure

Diagnosis: ECG: Faster rate with P waves followed by narrow QRS complexes.

Treatment:

- ***If patient is stable*** – No need for treatment, identify and treat the underlying cause.
- ***If the patient is hemodynamically unstable*** – there is a need for treatment.
- The patient should be kept in a quiet room

Mechanical treatment

  - Carotid sinus massage
  - Valsalva maneuver
  - Head immersion in cold water

Medial therapy:

  - β-blockers, Calcium channel blockers (Verapamil and Diltiazem) or digoxin can be helpful.

Atrial flutter: Rapidly fired signals cause the muscles in the atria to contract quickly, leading to a very fast, steady heartbeat. Is characterized by an atrial rate of 240-400 beat/min and is usually conducted to ventricles with block so that the ventricular rate is a fraction of the atrial rate. The block is usually regular so the ventricular rate is regular. Sometimes there may be a varying block resulting irregular ventricular beat.

Causes of atrial flutter: often associated with antecedent hear diseases

- Coronary artery diseases
- Pericarditis
- Valvular heart diseases
- Cardiomyopathy

ECG: Classic saw tooth pattern: 2 or 3 P waves are followed by QRS complex. The block is often in a ratio of 2:1 with an atrial rate of 240 beats/min and ventricular rate of 120 beat/min

Therapy:

- ***Drugs :***
    - Digoxin , Esmolol or Verapamil to control ventricular rate and
    - Quinidine or other ant arrhythmic agents to restore sinus rhythm.
- ***Direct current cardioversion:*** if the patient is hemodynamically unstable

Atrial Fibrillation: electrical signals in the atria are fired in a very fast and uncontrolled manner. Electrical signals arrive in the ventricles in a completely irregular fashion, so the heart beat is completely irregular.

Common cause of atrial fibrillation

- Stress , fever
- Excessive alcohol intake
- Hypotension
- Pericarditis
- Coronary artery disease
- Myocardial infarction
- Pulmonary embolism
- Mitral valve diseases : Mitral stenosis , Mitral regurgitation and Mitral valve prolapse
- Thyrotoxicosis
- Idiopathic (lone) atrial fibrillation.

ECG: irregularly irregular pattern disorganized atrial activity without discrete P wave.

Therapy

If the patient is hemodynamically unstable: direct current synchronous cardioversion:

If the patient is hemodynamically stable

- Identify and treat the underlying cause
- Control the ventricular rate :β-blockers , Calcium channel blockers (Verapamil and Diltiazim) , Digoxin
- Restore sinus rhythm : Quinidine
- Anticoagulants : if the atrial fibrillation ahs stayed for more than 1 week to prevent thromboembolism

Ventricular tachyarrhythmias:

Premature ventricular contractions (PVC) : is a type of arrhythmia in which occasional cardiac impulses are originating directly from the ventricles by passing the normal conduction system. These are among the commonest arrhythmias.

ECG: Wide and bizarre QRS appearing in a relatively normal looking ECG

Therapy: most isolated PVCs are benign and need no treatment.

Ventricular tachycardia: arises from the ventricles, it occurs paroxysmal and exceeds 120 beats/min, with regular rhythm. There is AV dissociation and the ventricular arrhythmia proceeds independently of the normal atrial rhythm. During ventricular tachycardia, the ventricles do not have enough time to relax, ventricular filling is impaired and the cardiac output significantly decreases. When ventricular tachycardia lasts for more than 30 seconds or requires control because of hemodynamic collapse it is called sustained Ventricular tachycardia.

ECG: Bizarre and wide QRS complexes coming in succession with no constant relation to P waves.

Therapy: since this is a life threatening situation urgent intervention is needed

- ***Anti-arrhythmic drugs***: intravenous administration of Beretylium, Lidocaine or Procainamide may be useful in returning the patient's rhythm to normal while preparation is being made for DC cardioversion.
- ***DC cardioversion***: is urgently required

Ventricular Fibrillation: electrical signals in the ventricles are fired in a very fast and uncontrolled manner, causing the heart to quiver rather than beat and pump blood. It is characterized by lack of ordered contraction of the ventricles. Therefore there is no cardiac out put. Thus ventricular fibrillation is synonymous with death unless urgent conversion to effective rhythm can be accomplished.

Therapy: patients need cardiorespiratory resuscitation

- Cardiac resuscitation
- Mechanical ventilation
- Cardiac compression and intracardiac adrenalin
- DC cardioversion using high voltage.

The place of Surgery in the management of Arrhythmias

- ♦ When an arrhythmia cannot be controlled by other treatments, there may be a place for surgery. After locating the heart tissue that is causing the arrhythmia, the tissue is altered or removed so that it will not produce the arrhythmia.

Prevention

If the precipitating factor for arrhythmia is identified, one has to avoid what is causing it.

E.g. If caffeine or alcohol is the cause, the patient has to avoid drinking coffee, tea, colas, or alcoholic beverages.

References:

1. Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Disordrs of cardiac rhythm , pages 1333-1357.

2. Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Cardiac arrhythmias, pages 7-14.

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CHAPTER FOUR
DISEASES OF THE KIDNEYS

1. Introduction to Renal Disease

Learning objectives: *at the end of this lesson the student will be able to:*

1. *List common etiologies of renal diseases.*
2. *Describe the calcification of renal diseases.*
3. *Identify common clinical manifestation of renal diseases.*
4. *Understand the diagnostic approach to renal diseases.*

- Patients with renal disease may have a variety of different clinical presentations.
- Some have symptoms that are directly referable to the kidney (gross hematuria, flank pain) or to associated extrarenal symptoms (edema, hypertension, signs of uremia).
- Many patients, however, are asymptomatic and are noted on routine examination to have an elevated plasma creatinine concentration or an abnormal urinalysis.
- Specific disorders are more likely to be either acute or chronic in duration, thereby narrowing the differential diagnosis among patients presenting with similar clinical findings related to the kidney.

Major causes of renal diseases.

Renal function is based upon four sequential steps, which are isolated to specific areas of the kidney or surrounding structures:

1. First, blood from the renal arteries is delivered to the glomeruli.
2. The glomeruli form an ultrafiltrate, which subsequently flows into the renal tubules.
3. The tubules reabsorb and secrete solute and/or water from the ultrafiltrate.
4. The final tubular fluid, the urine, leaves the kidney, draining sequentially into the renal pelvis, ureter, and bladder, from which it is excreted through the urethra.

The causes of renal disease are traditionally classified based on the portion of the renal anatomy most affected by the disorder

1. ***Prerenal disease*** – Reduced glomerular perfusion is most commonly caused by volume depletion and/or relative hypotension. This may result from:
    - True hypoperfusion due to bleeding, gastrointestinal, urinary, or cutaneous losses, or
    - Effective circulatory fluid volume depletion in congestive heart failure, shock, or cirrhosis.
2. ***Vascular disease*** – The vascular diseases affecting the kidney can be divided into those that produce acute and chronic disease.
    - The major acute causes are vasculitis, malignant hypertension, scleroderma, and thromboembolic disease.
    - The major chronic disorders are benign nephrosclerosis and bilateral renal artery stenosis.

3. Glomerular disease:

There are numerous idiopathic and secondary disorders that produce glomerular disease. Two general patterns (with considerable overlap in some diseases) are seen:

- The nephritic pattern which is associated with inflammation on histologic examination and produces an active urine sediment with red cells, white cells, granular and often cellular casts, and a variable degree of proteinuria;
- The nephrotic pattern which is not associated with inflammation on histologic examination and is primarily manifested clinically by proteinuria, often in the nephrotic range.

4. ***Tubular and interstitial disease*** – As with vascular disease, the tubular and interstitial diseases affecting the kidney can be divided into those that produce acute and chronic disease.
    - The most common acute tubulointerstitial disorders are acute tubular necrosis, which typically occurs in hospitalized patients, acute interstitial nephritis, which is often drug-induced, and cast nephropathy in multiple myeloma.
    - The major chronic tubulointerstitial disorders are polycystic kidney disease, vesicoureteral reflux, autoimmune disorders (such as sarcoidosis and Sjögren's syndrome), and analgesic abuse.
5. ***Obstructive uropathy*** – Obstruction to the flow of urine can occur anywhere from the renal pelvis to the urethra. The development of renal insufficiency in patients

without intrinsic renal disease requires bilateral obstruction and is most commonly due to prostatic disease.

Clinical manifestations – Patients with renal disease may present with a variety of clinical manifestations:

- Signs and symptoms resulting directly from alterations in kidney function, including decreased or no urine output, flank pain, edema, or discolored urine.
- Asymptomatic elevations in the plasma creatinine concentration or abnormalities on urinalysis.
- Symptoms and/or signs of renal failure, including anorexia, vomiting, mental status changes (including seizures), edema, and hypertension.
- The presence of certain symptoms or signs may suggest an underlying diagnosis.

  E.g.
  - Unilateral flank pain is most consistent with a renal stone, renal infarction, infection, or obstruction,
  - The total absence of urine (anuria) is primarily observed with bilateral ureteral obstruction or shock.
- A constellation of symptoms and signs may also favor a particular set of disorders.

  E.g. A patient with edema, hypertension, red to brown colored urine due to hematuria (with red cell casts), and a rapidly rising plasma creatinine concentration almost certainly has glomerulonephritis or vasculitis.
- Other manifestations, however, are relatively nonspecific and can be observed with a wide variety of disorders.

Disease duration: An important aspect of the evaluation of the patient with renal disease is the determination of disease duration. As noted above, the differential diagnosis can frequently be narrowed if the disease duration is known.

- ***Comparing the current urinalysis or plasma creatinine concentration with previous results: -*** A patient with a current plasma creatinine of 4.0 mg/dL (354 µmol/L) but a plasma level of 1.0 mg/dL (88 µmol/L) one month previously has acute disease while the same patient with a prior plasma creatinine concentration

of 3.0 mg/dL (265 µmol/L) two years ago has a slowly progressive chronic disease.

- When a previous urinalysis or plasma creatinine is unavailable, certain clinical elements may suggest the duration of disease. These include :
  - The recent onset of symptoms or signs, such as fever and discolored urine, suggests an acute process.
  - An increasing plasma creatinine after the initial evaluation is indicative of at least an acute component to the disease, while a stable value suggests a chronic disease. In addition, the rate of rise in the plasma creatinine concentration may help distinguish among possible disorders.

Diagnostic work up of patients with Renal Diseases.

1. **Assessment of renal function**– Once renal disease is discovered, the presence or degree of renal dysfunction should be assessed and the underlying disorder is diagnosed.
   - ***Glomerular filtration rate –*** An estimation of the glomerular filtration rate (GFR), usually by the plasma creatinine concentration and less often by the creatinine clearance, is used clinically to assess the degree of renal impairment and to follow the course of the disease. However, since all renal disorders variably affect renal function, estimation of the GFR has no diagnostic utility.

2. ***Urinalysis***: The urinalysis is the most important noninvasive test in the diagnostic evaluation, since characteristic findings on microscopic examination of the urine sediment strongly suggest certain diagnoses. E.g.
   - The finding of red cell casts is diagnostic of vasculitis or glomerulonephritis, and
   - The presence of muddy brown granular casts and epithelial cell casts in a patient with acute renal failure is highly suggestive of acute tubular necrosis;
   - Even a normal urinalysis has diagnostic utility.

Urine volume: has little diagnostic value.

- Anuria (Complete absence of urine output): may be due to shock, complete bilateral urinary tract obstruction, renal cortical necrosis, and bilateral vascular

occlusion (as with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome).

3. **Radiologic/imaging studies**. They are principally required to assess urinary tract obstruction, kidney stones, renal cyst or mass, disorders with characteristic radiographic findings, renal vascular diseases, and vesicoureteral reflux.

Renal ultrasonography:

- Showing small kidneys is most consistent with a chronic disease because of the progressive loss of renal parenchyma with time. However, the presence of normal-sized kidneys does not exclude chronic disease
- Obstructive uropathy: hydronephrosis, hydroureter, Stone, and the site of obstruction can be seen by U/S.

Plain film of the abdomen (KUB): A plain abdominal radiograph can detect renal stones and provide a rough approximation of kidney size and shape.

4. **Other studies:** may be ordered to make specific diagnosis
    1. Intravenous pyelogram
    2. Renal biopsy has limited value.

References:

1) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Clinical assessment of renal function, pages 279-280.

2. Acute Nephritic Syndrome

Learning objectives: *at the end of this lesson the student will be able to:*

1. *Define acute nephritic syndrome.*
2. *List the etiologies of acute nephritic syndrome..*
3. *Describe the clinical features and diagnostic approach to patients with acute nephritic syndrome.*
4. *Understand the pathogenesis of Poststreptococcal glomerulonephritis.*
5. *Identify the clinical manifestation of Poststreptococcal glomerulonephritis..*
6. *Identity complications of nephritic syndrome..*
7. *Understand the diagnostic approach to Poststreptococcal glomerulonephritis..*
8. *Understand the principle of management of Poststreptococcal glomerulonephritis.*

Definition

The acute nephritic syndrome is the clinical correlate of acute glomerular inflammation. In its most dramatic form, the acute nephritic syndrome is characterized by sudden onset (i.e., over days to weeks) of acute renal failure and oliguria (<400 mL of urine per day) associated with hypertension, edema and the presence of active urinary sediments.

Clinical features

- Extracellular fluid volume expansion, edema, and hypertension develop because of impaired GFR and enhanced tubular reabsorption of salt and water. Patients may present with congestive heart failure and pulmonary edema.
- And pictures of acute renal failure may also occur (see later sections).
- Evidence of the underlying cause can be detected (skin lesions, joint swelling, fever)

Laboratory tests

- Urinalysis: as a result of injury to the glomerular capillary wall, urinalysis typically reveals red blood cell casts, dysmorphic red blood cells, leukocytes, and subnephrotic proteinuria of <3.5 g per 24 h ("nephritic urinary sediment"). Hematuria is often macroscopic.
- Renal function test :Elevated level of serum creatinine
- Serology: Immunologic assays suggesting the underlying disease.

Etiology

Acute nephritic syndrome can result from renal-limited primary glomerulopathy or from secondary glomerulopathy complicating systemic disease. In general, rapid diagnosis and prompt treatment are critical to avoid the development of irreversible renal failure.

Immune-complex glomerulonephritis may be:

1. Idiopathic
2. Represent a response to a known antigenic stimulus (e.g., post infectious glomerulonephritis)
3. Part of a multisystem immune-complex disorder (e.g., lupus nephritis, Henoch-Schonlein purpura, cryoglobulinemia, bacterial endocarditis).

Poststreptococcal glomerulonephritis

Etiology and Epidemiology

- This is the prototypical postinfectious glomerulonephritis and a leading cause of acute nephritic syndrome.
- Most cases are sporadic, though the disease can occur as an epidemic. Glomerulonephritis develops, on average, 10 days after pharyngitis or 2 weeks after a skin infection (impetigo) with a nephritogenic strain of *group A β-hemolytic streptococcus*.
- Immunity to these strains is type-specific and long-lasting, and repeated infection and nephritis are rare. Epidemic poststreptococcal glomerulonephritis is most commonly encountered in children of 2 to 6 years of age with pharyngitis during the winter months. This entity appears to be decreasing in frequency, possibly due to more widespread and prompt use of antibiotics.
- Poststreptococcal glomerulonephritis in association with cutaneous infections usually occurs in a setting of poor personal hygiene or streptococcal superinfection of another skin disease.

Clinical picture

- The classic clinical presentation of poststreptococcal glomerulonephritis is full-blown nephritic syndrome with oliguric acute renal failure; however, most patients have milder disease.

- Indeed, subclinical cases outnumber overt cases by four- to tenfold during epidemics. Patients with overt disease present with gross hematuria (red or "smoky" urine), headache, and generalized symptoms such as anorexia, nausea, vomiting, and malaise.
- Swelling of the renal capsule can cause flank or back pain.

Physical examination*:* Hypervolemia, edema, and hypertension.

Complications;

- Congestive heart failure and Pulmonary edema
- Acute renal failure
- Sever hypertension with hypertensive encephalopathy.

Laboratory findings:

- ***Urinalysis:*** the urinary sediment is nephritic, with dysmorphic red blood cells, red cell casts, leukocytes, occasionally leukocyte casts, and subnephrotic proteinuria. Fewer than 5% of patients develop nephrotic-range proteinuria.
- ***Renal function test***: the serum creatinine is often mildly elevated at presentation.
- ***Serology:*** most patients (>90%) have circulating antibodies against streptococcal exoenzymes such as ASO, DNAase.

Diagnosis:

Acute poststreptococcal glomerulonephritis is usually diagnosed on clinical and serologic grounds. The characteristic lesion is diffuse proliferative glomerulonephritis.

Course and prognosis of the disease

- Poststreptococcal glomerulonephritis is typically an acute disease, with spontaneous recovery occurring in almost all patients, even those who develop renal insufficiency during the acute episode.
- Resolution of the clinical manifestations of poststreptococcal glomerulonephritis is generally quite rapid, assuming concurrent resolution of the infection**.**
- Diuresis typically begins within one week and the plasma creatinine concentration returns to the previous baseline by three to four weeks.
- Hematuria usually resolves within three to six months.
- The degree of proteinuria also falls during recovery, but at a much slower rate.
- Generally the long-term prognosis is good.

Treatment

1. Eliminating the streptococcal infection with antibiotics.
2. Supportive therapy until spontaneous resolution of glomerular inflammation occurs.
    a. Bed rest
    b. Salt restriction
    c. Diuretics and are employed to control extracellular fluid volume.
    d. Antihypertensive drugs to control high blood pressure
3. Dialysis : some patients may need dialysis

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3. Nephrotic syndrome:

Learning objectives: *at the end of this lesson the student will be able to:*

1. *Define nephrotic syndrome.*
2. *List the etiologies of nephrotic syndrome.*
3. *Describe the clinical features of nephrotic syndrome.*
4. *Identity complications of nephrotic syndrome..*
5. *Understand the diagnostic approach of nephrotic syndrome.*
6. *Understand the principle of management of nephrotic syndrome.*

Definition

The nephrotic syndrome is a clinical complex characterized by:

- Significant proteinuria of >3.5 g/1.73m^2/per 24 h (for practical purpose >3.0 to 3.5 g per 24 h) is the most important clinical feature
- Hypoalbuminemia
- Edema
- Hyperlipidemia and lipiduria and
- Hypercoagulability

Etiology

1. Multisystem diseases account for 50 –70 % of adult nephrotic syndrome.
    a. Diabetes mellitus
    b. Collagen vascular diseases
    c. Amyloidosis
2. Neoplasms: - leukemias, lymphomas and solid tumors
3. Infections: - viral, bacterial, protozoan and helimenthic
4. Primary glomerulopathies(Idiopathic): - account for 30 –50 % of adult nephrotic syndrome

Clinical picture

1. Proteinuria and hypoalbuminemia*:* - In general, the greater the proteinuria, the lower the serum albumin level. Hypoalbuminemia is compounded further by increased renal catabolism

and inadequate hepatic synthesis of albumin. The proteinuria is believed to be due to increased permeability of the glomerular basement membrane to proteins.

2. Edema*:* - Common sites for edema formation in the early stage include: dependent areas, face, peri-orbital areas and scrotum. Hypoalbuminemia and primary water and salt retention by kidneys are the postulated mechanisms for edema formation.

3. Hyperlipidemia*:* - is believed to be a consequence of increased hepatic lipoprotein synthesis & decreased clearance. Hyperlipidemia may accelerate atherosclerosis and progression of renal disease.

4. Hypercoagulability*: -*

- It is mutifactorial: some of the mechanisms are loss of anti-thrombin III in the urine, increased fibrinogen production by the liver , increased platelet aggregation.
- Spontaneous peripheral arterial or venous thrombosis, renal vein thrombosis, and pulmonary embolism may occur.
- Clinical features that suggest acute renal vein thrombosis include sudden onset of flank or abdominal pain, gross hematuria, a left-sided varicocele (the left testicular vein drains into the renal vein), increased proteinuria, and an acute decline in GFR. Chronic renal vein thrombosis is usually asymptomatic.

5. ***Other complications:*** *-*

- Protein malnutrition
- Iron-resistant microcytic hypochromic anemia due to transferrin loss.
- Hypocalcemia as a consequence of vitamin D deficiency due to enhanced urinary excretion of cholecalciferol-binding protein.
- An increased susceptibility to infection from urinary loss and increased catabolism of immunoglobulin.

Diagnosis

1. ***Confirming significant proteinuria***
   - Quantify 24 hours urine protein
   - Comparing with urinary creatinine level on a single void urine
   - Measurement of urinary protein by a dipstick (+3 or +4 diagnostic if the first two are not available)
2. ***Renal biopsy (if available*** *):* to identify the underlying histopathologic abnormality

- Minimal change diseases: accounts for 80 % nephrotic syndrome in children < 10 yrs.
- Membranous glomerulopathy: accounts for 60-70 % of nephrotic syndrome in adults.
- Focal segmental glomerulosclerosis

Treatment

The treatment of nephrotic syndrome involves:-

1. Specific treatment of the underlying morphologic entity
   - Minimal change disease : Steroids , and cytotoxic drugs
   - Membranous nephropathy : Not steroid responsive
2. Measures to control proteinuria: -
   a. Dietary protein restriction: the potential value of dietary protein restriction for reducing proteinuria must be balanced against the risk of contributing to malnutrition.
   b. Angiotensin-converting enzyme (ACE) inhibitors : decrease proteinuria by decreasing glomerular filtration pressure
   c. Controlling hypertension: keeping BP below 130/80 reduces proteinuria.
3. Treatment of complications of nephrotic syndrome.
   a. ***Edema***: should be managed cautiously by :
      i. ***Moderate salt restriction***, usually 1 to 2 g/day, and the judicious use of
      ii. ***Loop diuretics*** can be given in higher doses: It is unwise to remove >1.0 kg of edema per day as more aggressive diuresis may precipitate intravascular volume depletion and prerenal azotemia.
   b. ***Thromboembolism*** : Anticoagulation is indicated for patients with deep venous thrombosis, arterial thrombosis, and pulmonary embolism. Heparin may not be effective because of urinary loss of anti- thrombin III.
   c. ***Hyperlipidemia*** : may need lipid lowering agents
   d. ***Vitamin D deficiency***: Vit-- D supplementation.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Glomerular diseases, pages 1508-1515

2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Glomerular diseases, pages 296-307.

4. Acute Renal Failure

Learning objectives: at the end of this lesson the student will be able to **:**

1. *Define acute renal failure.*
2. *List the etiologies of acute renal failure.*
3. *Describe the pathophysiology of acute renal failure.*
4. *Identify the clinical manifestation of acute renal failure.*
5. *Identify complications of acute renal failure.*
6. *Understand the diagnostic approach of acute renal failure.*
7. *Understand the principles of management of acute renal failure.*
8. *Understand the course and prognosis of acute renal failure.*
9. *Refer patients with acute renal failure to hospitals with better facilities*

Definition:

Acute renal failure is a syndrome characterized by:

- Rapid decline in glomerular filtration rate (hours to days)
- Retention of nitrogenous wastes due to failure of excretion
- Disturbance in extracellular fluid volume and
- Disturbance electrolyte and acid base homeostasis.

Based on the amount of urine output acute renal failure may be classified as

- ***Anuric:*** - if urine volume is less than 100 ml/day
- ***Oliguric:*** - if urine volume is less than 400 ml/day
- ***Non-oliguric****:* - if urine volume is greater than or equal 400 ml/day

Epidemiology: -

- ARF complicates approximately 5% of hospital admissions and up to 30% of admissions to intensive care units. Oliguria (urine output < 400 ml/d) is a frequent but not invariable clinical feature (~50%).
- ARF is usually asymptomatic and is diagnosed when biochemical screening of hospitalized patients reveals a recent increase in plasma urea and creatinine concentrations.
- Most ARF is reversible, the kidney being relatively unique among major organs in its ability to recover from almost complete loss of function.

- Nevertheless, ARF is associated with major in-hospital morbidity and mortality, in large part due to the serious nature of the illnesses that precipitate the ARF.
- A prospective study in Ethiopian patients done by Worku Zewdu in 1992, sowed that septic abortion was the leading cause of ARF followed by *P.falciparum* malaria and nephrotoxic agents.

Acute renal failure may complicate a wide range of diseases, which for purposes of diagnosis and management are conveniently divided into three categories

Etiologic classification of acute renal failure

A. ***Prerenal ARF*** : account for nearly 55 % of all cases of acute renal failure

I. Hypovolemia

- Hemorrhage, burns, dehydration
- Gastrointestinal fluid loss: vomiting, surgical drainage, diarrhea
- Renal fluid loss: diuretics, osmotic diuresis (e.g., diabetes mellitus), hypoadrenalism
- Sequestration in extravascular space: pancreatitis, peritonitis, trauma, burns, severe hypoalbuminemia

II. Low cardiac output

- Diseases of myocardium, valves, and pericardium; arrhythmias; tamponade
- Other: pulmonary hypertension, massive pulmonary embolus

III. Altered renal systemic vascular resistance ratio

- Systemic vasodilatation: sepsis, anaphylaxis IV. Renal hypoperfusion with impairment of renal autoregulatory responses
- NSAIDS, angiotensin-converting enzyme inhibition

B. Intrinsic Renal ARF: account for nearly 40% of all ARF

I. Renovascular obstruction (bilateral or unilateral in the setting of one functioning kidney)

II. Disease of glomeruli or renal microvasculature

III. Acute tubular necrosis

- ***Ischemia:*** as for prerenal ARF (hypovolemia, low cardiac output, renal vasoconstriction, systemic vasodilatation), obstetric complications (abruptio placentae, postpartum hemorrhage)
- *Toxins*

- Exogenous: radio contrast, cyclosporine, antibiotics (e.g., aminoglycosides), chemotherapy (e.g., cisplatin), organic solvents (e.g., ethylene glycol), acetaminophen, illegal abortifacients
- Endogenous: rhabdomyolysis, hemolysis, uric acid, oxalate, plasma cell dyscrasia (e.g., myeloma)

IV. *Interstitial nephritis*

***Post renal ARF (OBSTRUCTION)*:** account for ~5% of ARF.

I. Ureteric

- Calculi, blood clot, sloughed papillae, cancer, external compression (e.g., retroperitoneal fibrosis)

II. Bladder neck

- Neurogenic bladder, prostatic hypertrophy, calculi, cancer, blood clot

III. Urethra

- Stricture, congenital valve, phimosis

Prerenal ARF

- Prerenal ARF is the most common form of ARF and represents a physiologic response to mild to moderate renal hypo perfusion.
- Prerenal ARF is rapidly reversible upon restoration of renal blood flow and glomerular ultrafiltration pressure.
- More severe hypoperfusion may lead to ischemic injury of renal parenchyma and intrinsic renal ARF. Thus, prerenal ARF and intrinsic renal ARF due to ischemia are part of a spectrum of manifestations of renal hypoperfusion.
- Prerenal ARF can complicate any disease that induces hypovolemia, low cardiac output, systemic vasodilatation, or selective renal vasoconstriction.

Pathophysiology:

- *Hypovolemia* leads to glomerular hypoperfusion, but filtration rate are preserved during mild hypoperfusion through several compensatory mechanisms. During states of more severe hypoperfusion, these compensatory responses are overwhelmed and GFR falls, leading to prerenal ARF.
- Drugs that interfere with adaptive responses in the renal microcirculation may convert compensated renal hypoperfusion into overt prerenal ARF or trigger progression of prerenal ARF to ischemic intrinsic renal ARF (ACE-inhibitors, NSAIDS)

Intrinsic ARF

- Intrinsic renal ARF can complicate many diverse diseases of the renal parenchyma.
- Most intrinsic renal ARF is triggered by ischemia (ischemic ARF) or nephrotoxins (nephrotoxic ARF), insults that classically induce acute tubular necrosis (ATN).

Diagnosis of ARF:

Careful history is essential

- Exposure to nephrotoxins and drugs
- Anuria may indicate post-renal causes
- Skin rashes may indicate allergic nephritis
- Evidences of volume depletion: diarrhea, bleeding
- Pelvic and per-rectal examination: look for evidence of abortion
- Ischemia or trauma to the legs or arms may indicate rhabdomyolysis
- Recent surgical or radiologic procedures
- Past and present use of medications
- Family history of renal diseases

Physical examination: should be focused to rule out possible differential diagnosis

Prerenal ARF: is suggested by clinical signs of

- Intravascular volume depletion (e.g. orthostatic hypotension , rapid pulse and poor skin turgor)
- Congestive heart failure (e.g. raised JVP , S3 , dependent edema , and pulmonary rales)

Acute allergic interstitial nephritis: is suggested by signs of allergy (e.g. periorbital edema, esosinophilia , maculopapular rash , and wheezing)

Lower Urinary tract obstruction: is suggested by suprapubic or flank mass or symptoms of bladder dysfunction (e.g. hesitancy, urgency)

Uremia*:* - clinical syndrome resulting from the adverse effect of renal failure on other organ systems (only very few develop in acute renal failure)

Complications of ARF

- ***Intravascular overload:*** may be recognized by weight gain , hypertension , elevated central venous pressure (raise JVP) , Pulmonary edema

- ***Electrolyte disturbance***
    - ***Hyperkalemia:*** (serum K^+ >5.5 mEq/L) develops as a result of decreased renal excretion combined with tissue necrosis or hemolysis.
    - ***Hyponitremia :*** (serum Na^+ concentration < 135 mEq/L) results from excessive water intake in the face of excretory failure
    - ***Hyperphosphatemia :*** (serum Phosphate concentration of > 5.5 mg /dl) results from failure of excretion or tissue necrosis
    - ***Hypocalcemia :*** (serum Ca^{++} < 8.5 mg/dl) results from decreased Active Vit-D , hyperposhphatemia , or hypoalbuminemia
    - ***Hypercalcemia:*** (serum Ca^{++} > 10.5 mg /dl) may occur during the recovery phase following rhabdomyolysis induced acute renal failure.
- ***Metabolic acidosis :*** (arterial blood PH < 7.35) is associated with sepsis or sever heart failure
- ***Hyperuricemia:*** due to decreased uric acid excretion
- ***Bleeding tendency :*** may occur due to platelet dysfunction and coagulopathy associated with sepsis
- ***Seizure: may occur related to uremia***
- ***Chronic Renal failure:*** a modest degree of decline in filtration may exist in 10 % of patients for several months following ARF. In patients with underlying renal diseases who experience ARF , progression to chronic renal failure is relatively likely.

Diagnostic work up

1. Urinalysis: Microscopic evaluation of urinary sediment.

- Presence of few formed elements or hyaline casts is suggestive of prerenal or postrenal azotemia.
- Many RBCs may suggest calculi , trauma , infection or tumor
- Eosinophilia : occurs in 95 % of patients with acute allergic nephritis
- Brownish pigmented cellular casts and many renal epithelia cells are seen in patients with acute tubular necrosis (ATN)
- Pigmented casts without erythrocytes in the sediment from urine but with positive dipstick for occult blood indicates hemoglobinuria or myoglobinuria

- Dipstick test: trace or no proteinuria with pre-renal and post-renal ARF; mild to moderate proteinuria with ATN and moderate to severe proteinuria with glomerular diseases.
- RBCs and RBC casts in glomerular diseases
- Crystals RBCs and WBCs in post-renal ARF.

2. ***Urine and blood Chemistry:*** most of these tests help to differentiate prerenal azotemia, in which tubular reabsorption function is preserved from acute tubular necrosis where tubular reabsorption is severely disturbed.
   - Osmolality or specific gravity: decreased in ATN and pos-renal ARF (urine is diluted) , while increased in pre-renal ARF (urine is concentrated .)
   - BUN/plasma creatinine ratio: the BUN/plasma creatinine ratio is normal at 10-15:1 in ATN, but may be greater than 20:1 in prerenal disease due to the increase in the passive reabsorption of urea that follows the enhanced proximal transport of sodium and water. Thus, a high ratio is highly suggestive of prerenal disease as long as some other cause is not present. But this criterion is not highly specific.
   - Renal failure index: ratio of urine Na^+ to urine to plasma creatinine ratio ($U_{Na}/U_{cr}/P_{cr}$) . Values less than 1 % are consistent with prerenal ARF ,where as a value > 1% indicates ATN
   - Fractional excretion of Na^+: is ration of urine-to-plasma Na ratio to urine-to-plasma creatinine expressed as a percentage [$(U_{Na}/P_{Na})/(U_{cr}/P_{cr})$X 100]. Value below 1% suggest prerenal failure , and values above 1% suggest ATN
   - Serum K^+ and other electrolytes
3. ***Radiography/imaging***
   - ***Ultrasonography:*** helps to see the presence of two kidneys, for evaluating kidney size and shape, and for detecting hydronephrosis or hydroureter. It also helps to see renal calculi, and renal vein thrombosis.
   - ***Retrograde pyelography:*** is done when obstructive uropathy is suspected

Management of Acute renal failure:

1. Prevention:

- Because there are no specific therapies for ischemic or nephrotoxic ARF, prevention is of paramount importance.

- Many cases of ischemic ARF can be avoided by close attention to cardiovascular function and intravascular volume in high-risk patients, such as the elderly and those with preexisting renal insufficiency.
- Indeed, aggressive restoration of intravascular volume has been shown to reduce the incidence of ischemic ARF dramatically after major surgery or trauma, burns, or cholera.
- The incidence of nephrotoxic ARF can be reduced by tailoring the dosage of potential nephrotoxins to body size and GFR; for example, reducing the dose or frequency of administration of drugs in patients with preexisting renal impairment.

2. Preliminary measures

- ***Exclusion of reversible causes***: Obstruction should be relived , infection should be treated
- ***Correction of prerenal factors***: intravascular volume and cardiac performance should be optimized
- ***Maintenance of urine output***: although the prognostic importance of oliguria is debated, management of nonoliguric patients is easier. Loop diuretics may be usefully to convert the oliguric form of ATN to the nonoliguric form. High doses of loop diuretics such as Furosemide (up to 200 to 400 mg intravenously) may promote diuresis in patients who fail to respond to conventional doses.

***3. Specific Therapies*:**

- To date, there are no specific therapies for established intrinsic renal ARF due to ischemia or nephrotoxicity.
- Management of these disorders should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of additional insults, and prevention and treatment of complications.
- Specific treatment of other causes of intrinsic renal ARF depends on the underlying pathology.

***Prerenal ARF*:**

- The composition of replacement fluids for treatment of prerenal ARF due to hypovolemia must be tailored according to the composition of the lost fluid.
- Severe hypovolemia due to hemorrhage should be corrected with packed red blood cells, whereas isotonic saline is usually appropriate replacement for mild to moderate hemorrhage or plasma loss (e.g., burns, pancreatitis).

- Urinary and gastrointestinal fluids can vary greatly in composition but are usually hypotonic. Hypotonic solutions (e.g., 0.45% saline) are usually recommended as initial replacement in patients with prerenal ARF due to increased urinary or gastrointestinal fluid losses, although isotonic saline may be more appropriate in severe cases.
- Subsequent therapy should be based on measurements of the volume and ionic content of excreted or drained fluids. Serum potassium and acid-base status should be monitored carefully.

Postrenal ARF:

- Management of postrenal ARF requires close collaboration between nephrologist, urologist, and radiologist.
- Obstruction of the urethra or bladder neck is usually managed initially by transurethral or suprapubic placement of a bladder catheter, which provides temporary relief while the obstructing lesion, is identified and treated definitively.
- Similarly, ureteric obstruction may be treated initially by percutaneous catheterization of the dilated renal pelvis or ureter.

4. Supportive Measures: (Conservative therapy)

- ***Dietary management:*** adequate calorie intake is essential in patients with ARF.
    - Generally, sufficient calorie reflects a diet that provides 40-60 gm of protein and 35-50 kcal/kg lean body weight.
    - In some patients, severe catabolism occurs and protein supplementation to achieve 1.25 gm of protein /kg body weight is required to maintain nitrogen balance.
    - Restricting dietary protein to approximately 0.6 g/kg per day of protein of high biologic value (i.e., rich in essential amino acids) may be recommended in sever azotemia.
- ***Fluid and electrolyte management*** :

  Following correction of hypovolemia, total oral and intravenous fluid administration should be equal to daily sensible losses (via urine, stool, and NG tune o surgical drainage) plus estimated insensible (i.e. , respiratory and derma) losses which usually equals 400 – 500 ml/day. Strict input output monitoring is important.
- ***Hypervolemia***: can usually be managed by restriction of salt and water intake and diuretics.

- ***Metabolic acidosis***: is not treated unless serum bicarbonate concentration falls below 15 mmol/L or arterial pH falls below 7.2.
    - More severe acidosis is corrected by oral or intravenous sodium bicarbonate. Initial rates of replacement are guided by estimates of bicarbonate deficit and adjusted thereafter according to serum levels.
    - Patients are monitored for complications of bicarbonate administration such as hypervolemia, metabolic alkalosis, hypocalcemia, and hypokalemia.
    - From a practical point of view, most patients requiring sodium bicarbonate need emergency dialysis within days.
- ***Hyperkalemia:*** cardiac and neurologic complications may occur if serum K^+ level is > 6.5 mEq/***L***
    - Restrict dietary K^+ intake
    - Give calcium gluconate 10 ml of 10% solution over 5 minutes
    - Glucose solution 50 ml of 50 % glucose plus Insulin 10 units IV
    - Give potassium –binding ion exchange resin
    - Dialysis: it medial therapy fails or the patient is very toxic
- ***Hyperphosphatemia*** is usually controlled by restriction of dietary phosphate and by oral aluminum hydroxide or calcium carbonate, which reduce gastrointestinal absorption of phosphate.
- ***Hypocalcemia*** does not usually require treatment.
- ***Anemia***: may necessitate blood transfusion if severe or if recovery is delayed.
- ***GI bleeding***: Regular doses of antacids appear to reduce the incidence of gastrointestinal hemorrhage significantly and may be more effective in this regard than H2 antagonists, or proton pump inhibitors.
- Meticulous care of intravenous cannulae, bladder catheters, and other invasive devices is mandatory to avoid infections

Dialysis

Indications and Modalities of Dialysis: - Dialysis replaces renal function until regeneration and repair restore renal function. Hemodialysis and peritoneal dialysis appear equally effective for management of ARF. Absolute indications for dialysis include:

- Symptoms or signs of the uremic syndrome
- Refractory hypervolemia

- Sever hyperkalemia
- Metabolic acidosis.

Clinical course and prognosis

- Stages: acute renal failure due to ATN typically occurs in three stages: Azotemic , Diuretic , and recovery phases. The initial azotemic stage can be either oliguric or non oliguric type.
- Morbidity and mortality: are affected by the presence of oliguria
  - GI bleeding, septicemia, metabolic acidosis and neurologic abnormalities are more common in oliguric patients than in nonoliguric patients.
  - The mortality rate for oliguric patients is 50 % where as that of nonoliguric patients is only 26 %

Prognosis:

- The mortality rate among patients with ARF approximates 50. It should be stressed, however, that patients usually die from sequelae of the primary illness that induced ARF and not from ARF itself
- Mortality is affected by both severity of the underlying diseases and the clinical setting in which acute renal failure occurs
- E.g. the mortality of ATN is 60 % when it results from surgery or trauma, 30 % when it occurs as a complication of medical illnesses, and 10-15 % when pregnancy is involved.
- Ischemia associated ATN has 2X the mortality risk of nephrotoxic ATN.
- In agreement with this interpretation, mortality rates vary greatly depending on the cause of ARF: ~15% in obstetric patients, ~30% in toxin-related ARF, and ~60% following trauma or major surgery.
- Oliguria (<400 mL/d) at time of presentation and a rise in serum creatinine of >3 mg/dl are associated with a poor prognosis and probably reflect the severity of renal injury and of the primary illness.
- Mortality rates are higher in older debilitated patients and in those with multiple organ failure
- Patients with no complicating factors who survive an episode of acute renal failure have a 90 % chance of complete recovery of kidney function.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Acute renal failure, pages 1644-1652.

2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Acute renal failure, pages 280-284.

5. Chronic Renal Failure

Learning objectives: at the end of this lesson the student will be able to **:**

1. *Define chronic renal failure.*
2. *List the etiologies of chronic renal failure.*
3. *Describe the pathophysiology of chronic renal failure.*
4. *Identify the clinical manifestation of chronic renal failure.*
5. *Identify common complications of chronic renal failure.*
6. *Understand the diagnostic approach of chronic renal failure.*
7. *Understand the principles of management of chronic renal failure.*
8. *Understand the course and prognosis of chronic renal failure.*
9. *Refer patients with Chronic renal failure to better facilities,*

Definitions

Chronic Renal failure : progressive and irreversible reduction of the renal function, over a period of more than 6 months, to a level less than 20 % of the normal, as a result of destruction of significant number of nephrons.

- ***End stage renal disease (ESRD):*** represents a clinical state or condition in which there has been an irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependent upon renal replacement therapy (dialysis or transplantation) in order to avoid life-threatening uremia.
- **Uremia** is the clinical and laboratory syndrome, reflecting dysfunction of all organ systems as a result of untreated or undertreated acute or chronic renal failure.
- ***Azotemia*** refers to the retention of nitrogenous waste products as renal insufficiency develops.

Etiologies

1. *Prerenal causes*

- *Sever long standing renal artery stenosis*
- *Bilateral renal artery embolism*

2. Renal causes

- *Chronic glomerulonephritis:* - primary or secondary forms (30%)

- *Chronic tubulointerstitial disease:* - vesicouretral reflux, and chronic pyelonephritis (in adolescents)
- *Vascular disease:* - hypertensive nephrosclerosis
- Diabetic nephropathy
- Connective tissue diseases : SLE , scleroderma
- *Hereditary disease:* -polycystic kidney disease

3. Post renal cause

- *Obstructive nephropathy:* - urolithiasis, benign prostatic hypertrophy,

❖ Chronic glomerulonephritis , Hypertension and diabetic nephropathy are the commonest causes for ESRD

Stages of Chronic renal failure

1. ***Stage of decreased renal reserve***
   - Basal glomerular filtration rate (GFR) may be normal or even elevated (hyper-filtration). Adaptation increases the function of the remaining nephrons
   - Patients are symptom free
   - BUN and creatinine are normal or slightly elevated.
2. ***Stage of Renal insufficiency***
   - *GFR declines by 70 % (i.e., GFR will be 30% of normal)*
   - Patients may remain asymptomatic
   - Biochemical evidence of the decline in GFR, i.e., rise in serum concentrations of urea and creatinine. Early additional clinical and laboratory manifestations of renal insufficiency may occur. These may include nocturia, mild anemia and loss of energy, decreasing appetite and early disturbances in nutritional status.
   - Sudden stress such as infection, urinary tract obstruction, dehydration, administration of nephrotoxic drugs may induce signs and symptoms of uremia.
3. ***Renal failure***
   - *GFR falls to below 30% of normal*
   - *A*n increasing number and severity of uremic clinical manifestations
   - Biochemical abnormalities raised NUN and creatinine.
4. ***End stage renal diseases (ESRD)***
   - *GFR falls below 5 to 10% of normal*

- Continued survival without renal replacement therapy becomes impossible.

Pathophysiology

- Uremic manifestations occur mainly due to accumulation of nitrogenous wastes and the reason for accumulation of these wastes is decreased renal excretion and reduced catabolizing capacity of the kidney
- Most toxins in uremia are by products of proteins and amino acid metabolism, because unlike carbohydrates and fats, which are metabolized to CO_2 and H_2O, which can be excreted through the lungs and skin , by products of protein are non volatile organic acids

Clinical manifestations and complications of Chronic Renal failure

1. ***Fluid, electrolyte and acid base disturbance***

a) Volume expansion and contraction (edema, dehydration)

- As long as water intake does not exceed the capacity for free water clearance, the extra cellular fluid volume expansion will be isotonic and the patient will remain normonatremic. On the other hand, hyponatremia will be the consequence of excessive water ingestion.
- Patients with CRF also have impaired renal mechanisms for conserving Na+ and H_2O. When an extra renal cause for fluid loss is present (e.g., vomiting, diarrhea, sweating, fever), these patients are prone to volume depletion and dehydration.
- In the face of Sodium intake patients may retain Na^+ and water which may lead to congestive heart failure, eripheral edema and ascites .

b) Potassium Homeostasis: -

- Most commonly, clinically significant hyperkalemia does not occur until the GFR falls to below 10 mL/min
- Factors that contribute to increased serum K^+ level are
- Endogenous a K^+ load (e.g., hemolysis, trauma, infection) or
- Exogenous K^+ (e.g., administration of stored blood, K^+-containing medications, K^+-containing dietary salt substitute).
- Acidosis : facilitates influx of K^+ form ICF to ECF
- Drugs: potassium sparing diuretics, ACE inhibitors.

c) Metabolic Acidosis: -

- Acidosis is a common disturbance during the advanced stages of CRF. With advancing renal failure, total urinary net daily acid excretion is usually reduced markedly.

2. Renal osteodetrophy and Metabolic bone disease:

- Is due to disturbance in bone phosphate and calcium metabolism.
- Hyperphosphatemia is a feature of advanced renal failure. The serum phosphate concentration rises in patients with a GFR < 20 mL/min.
- *Calcium*: - The total plasma Ca^{2+} concentration in patients with CRF is often significantly lower than normal. Patients with CRF tolerate the hypocalcaemia quite well; rarely is a patient symptomatic from the decreased Ca^{2+} concentration. Note that the low serum level of Ca^{++} is attributed to secondary hyperparathyroidism.
- Reduced synthesis of 1,25 (OH)2D3 during CRD plays a key role in the pathogenesis of hyperparathyroidism, both directly and through hypocalcaemia. The abnormal vitamin D metabolism may be related to the renal disease itself (since the active vitamin D metabolite is normally produced in the proximal tubule) and to the hyperphosphatemia, which has a suppressive effect on the renal 1α-hydroxylase enzyme.

Some of the resulting bony abnormalities are

- ***Ostitis fibrosa cystica*** : is due to osteoclastic bone resorption of specially terminal phalanges , long bones and distal end of clavicle
- ***Renal rickets (Osteomalacia)***
- ***Osteosclerosis*** : enhanced bone density in the upper and lower margins of vertebrae

3. Cardiovascular complications

a) ***Congestive heart failure and/or pulmonary edema*** : it may be due to

- Volume over load
- Increase pulmonary capillary permeability

b) Hypertension :

- Is the most common complication of end stage renal disease.
- It results from fluid overload.

- Sometimes sever form of hypertension may occur.

c) *Pericarditis:* metabolic toxins are responsible for pericarditis.

- The finding of a multicomponent friction rub strongly supports the diagnosis
- The pericardial effusion is often hemorrhagic

4. Hematologic abnormalities :

a) Normocytic normochromic anemia : which may be severe (Hgb 4-6 gm/dl)

The cause of anemia is multifactorial

- Decreased synthesis of erythropoietin (the most important factor)
- Toxins suppressing bone marrow function
- Blood loss (mainly GI blood loss)
- Decreased life span of RBC

b) ***Bleeding tendency*** : attributed to platelet dysfunction

- Patients may manifest with bleeding and easily bruiseablity
- GI bleeding
- Intracranial hemorrhage

c) ***Susceptibility to infection***: is due to

- Change in leukocyte formation and function
- Lymphocytopeneia and atrophy of lymphoid tissue

5. Neuromuscular abnormalities

Early stage: irritability, inability to concentrate drowsiness, insomnia

Intermediate stage:

- Mild behavioral change , poor judgment
- Neuromuscular irritability: hiccup , cramps , fasciculation , twitching of muscles

Terminal stage:

- Asterixis, myoclonus, chorea, seizure
- Stupor which may even lead to coma
- Peripheral neuropathy : distal sensory polyneuropathy
    - Restless leg syndrome : ill defined sensation of discomfort on the legs

6. Gastro intestinal abnormalities

- Early symptoms : anorexia , hiccup , nausea and vomiting
- Uremic fetor: the patient's breathe smells like urine.
- Mucosal ulceration leads to GI bleeding and peptic ulcer diseases.

7. Endocrine and Metabolic abnormalities

- Hypogonadism is common
    - In men : decreased plasma testosterone level , impotence m oligospermia
    - In women: amenorrhea, inability to carry pregnancy to term.

8. Dermatologic abnormalities ;

- Pallor due to anemia
- Echymosis, hematoma
- Pruritis, and excoriation (Ca^{++} deposits and 2^0 hyperparathyroidism)
- Yellowish declaration of skin : urochromes
- Uremic frost: is seen in advanced uremia
    - It is due to high concentration of urea in the sweat, and after evaporation of the sweat, a fine white powder can be found on the skin surface.

Diagnostic approach

***Differentiate acute from chronic renal failure*:** the following findings characterize CRF

- Reduced kidney size on ultrasonography
- Long standing nocturia and pruritis
- Finding of broad tubular casts on urine analysis
- Anemia (not always)
- Renal osteodystrophy

Identification of aggravating factors (acute or chronic)

- Hypovolemia or hypotension
- Hypertension
- Congestive heart failure
- Sepsis
- Nephrotoxins

Evaluation of reversible underlying etiology

- Malignant hypertension
- Obstructive uropathy
- Systemic lupus erythematosis

Establishing the underlying cause

History

- Of special importance in establishing the etiology of CRF are a history of:
    - Hypertension
    - Diabetes mellitus
    - Systemic infectious or inflammatory diseases
    - Metabolic diseases
    - Exposure to drugs and toxins
    - Family history of renal and urologic disease.
- In evaluating the uremic syndrome, questions about appetite, diet, nausea, and vomiting, hiccoughing, shortness of breath, edema, weight change, muscle cramps, bone pain, mental acuity, and activities of daily living are especially helpful.

Physical Examination: -

- Particular attention should be paid to:
- Blood pressure
- Funduscopy
- Precordial examination
- Examination of the abdomen for bruits and palpable renal masses
- Extremity examination for edema
- Neurologic examination for the presence of asterixis, muscle weakness, and neuropathy
- In addition, the evaluation of prostate size in men and potential pelvic masses in women should be undertaken by appropriate physical examination.

Diagnostic work up

- These should also focus on a search for clues to an underlying disease process and its continued activity.
- Other tests to determine the severity and chronicity of the disease include :
    - Serial measurements of serum creatinine and blood urea nitrogen
- ***Hemoglobin***
- ***Electrolytes***: calcium, phosphate, and alkaline phosphates to assess metabolic bone disease.
- ***Urinalysis:***

- May be helpful in assessing the presence of ongoing activity of the underlying inflammatory or proteinuric disease process, and when indicated should be supplemented by a 24-h urine collection for quantifying protein excretion.
- The presence of broad casts on examination of the urinary sediment is a nonspecific finding seen with all diverse etiologies and reflects an advanced stage of CRF.

- ***Ultrasonography of kidneys:***
  - An ultrasound examination of the kidneys verifies the presence of two symmetric kidneys, provides an estimate of kidney size, and rules out renal masses and obstructive uropathy.
  - The documentation of symmetric small kidneys supports the diagnosis of progressive CRF with an irreversible component of scarring. The occurrence of normal kidney size suggests the possibility of an acute rather than chronic process. However in some diseases, chronic renal failure may be present with normal sized or even enlarged kidneys. E.g. Amyloidosis , polycystic kidney diseases , Diabetic nephropathy

Management of chronic renal failure The general management of the patient with chronic renal disease involves the following issues

1) Treatment of reversible causes of renal dysfunction
2) Preventing or slowing the progression of renal disease
3) Treatment of the complications of renal dysfunction
4) Identification and adequate preparation of the patient in whom renal replacement therapy will be required

1. ***Treating reversible causes of renal dysfunction*** – In addition to exacerbation of their original renal disease, patients with chronic renal disease, with a recent decrease in renal function may be suffering from an underlying reversible process such as *:*
   - *Hypotension or dehydration*
   - *Administration of nephrotoxic drugs*
   - *Urinary tract obstruction*

- *Sever hypertension*
- *Infection*

- Correcting these reversible causes can improve the renal function.

2. ***Slowing the rate of progression of renal diseases***:
   - Angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) slows the progression of chronic renal failure .
   - Blood pressure control : decreases progression of CRF

   Target BP for patients with:
   - Proteinuria is 125/75 mmHg
   - for patients without proteinuria is 130/85 mmHg

   - The possible efficacy of dietary protein restriction, in slowing progression of renal diseases, is less clear.

3. ***Treatment of the complications of renal dysfunction*** :

a) ***Volume overload*** –
- Dietary sodium restriction
- Diuretic therapy, usually with a loop diuretic given daily.

b) ***Hyperkalemia***:
- Low-potassium diet or concurrent use of a loop diuretic (to increase urinary potassium losses) often ameliorates the degree of hyperkalemia.
- Calcium gluconate ; 10 ml of 10% solution over 5 minutes
- Glucose plus insulin:
- Correction of acidosis : administration of bicarbonate
- Potassium exchange resins: Kayaxalate

c) Metabolic acidosis :
- Alkali therapy is advocated to maintain the plasma bicarbonate concentration above 22 mEq/L. If alkali is given, sodium bicarbonate (in a daily dose of 0.5 to 1 mEq/kg per day) is the agent of choice.

d) Hyperphosphatemia:
- Dietary phosphate restriction may limit the development of secondary hyperparathyroidism in patients with chronic renal failure. An intake of

about 800 mg/day may be desirable but can be accomplished only by limiting protein intake.

e) *Hypertension*:

- Salt restriction
- Diuretics: loop diuretics are recommended for the treatment of hypertension and edema in patients with chronic renal failure. Thiazide diuretics have additive effect when administered with a loop diuretic for refractory edema.
- Anti hypertensive drugs

f) Anemia*:*

- Blood transfusion in selected patients
- Recombinant Erythropoietin may be given.

g) Malnutrition:

- The desire to maintain adequate nutrition among patients with chronic renal failure clearly competes with attempts to slow the progression of renal dysfunction with the use of a low protein diet.
- Although the benefits of slowing progressive renal failure with marked dietary protein restriction remain controversial, it is probably reasonable to restrict intake to 0.8 to 1.0 g/kg of high biologic value protein (plant source)
- Since this level of restriction avoids protein malnutrition and may slow progressive disease. Overall, the diet of most patients with chronic renal failure should provide approximately 30 to 35 kcal/kg per day.

4. Preparation for renal replacement Therapy

- Education
- Informed choice of renal replacement therapy
    i. Chronic Hemodialysis
    ii. Kidney transplantation

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Chronic renal failure, pages 1653-1662.

2) Myers R. Allen , National Medical Series for independent Study (NMS) 3rd edition Medicine, Chronic renal failure, pages 285-286.

6. Urinary Tract infection

***Learning Objective**: At the end of this unit the student will be able to*

1. *Define urinary tract infections.*
2. *List the etiologies of urinary tract infections.*
3. *Describe the epidemiology of urinary tract infections.*
4. *Explain the pathogenesis of urinary tract infections.*
5. *Describe the clinical features of urinary tract infections.*
6. *List the common complications urinary tract infections.*
7. *Describe the most commonly used tests for the diagnosis of urinary tract infections.*
8. *Make an accurate diagnosis of urinary tract infections.*
9. *Treat urinary tract infections with appropriate antibiotics.*
10. *Design appropriate methods of prevention and control of urinary tract infections.*

Definitions

UTI: is an acute infection of the urinary tract, and is subdivided into two general anatomic categories:

- L*ower urinary tract infection: which includes urethritis and cystitis and*
- *Upper urinary tract infection: includes acute pyelonephritis, prostatitis, and intrarenal and perinephric abscesses).*

From a microbiologic perspective, urinary tract infection (UTI)

- Exists when pathogenic microorganisms are detected in the urine, urethra, bladder, kidney, or prostate. In most instances, growth of more than 10^5 organisms per milliliter from a properly collected midstream "clean-catch" urine sample indicates infection.
- Especially in symptomatic patients, a smaller number of bacteria (10^2 to 10^4/mL) may signify infection.
- In urine specimens obtained by suprapubic aspiration or "in-and-out" catheterization and in samples from a patient with an indwelling catheter, colony counts of 10^2 to 10^4/mL generally indicate infection.

Recurrence of UTI after treatment

- Infections that recur after antibiotic therapy can be due to the persistence of the originally infecting strain (as judged by species, antibiogram, serotype, and molecular

type) that become evident within 2 weeks of cessation of therapy termed relapse, or to reinfection with a new strain that become evident after 2 weeks of cessation of therapy.

Chronic pyelonephritis: refers to chronic interstitial nephritis believed to result from bacterial infection of the kidney. Manifested by calyceal dilatation & cortical scarring.

Acute Urinary tract infection

Epidemiology

Epidemiologically, UTIs are subdivided into:

1. Non-catheter-associated (or community-acquired) infections.
2. Catheter-associated (or nosocomial) infections and

- The vast majority of acute symptomatic infections involve young women.
- Acute symptomatic UTIs are unusual in men under the age of 50.
- The development of asymptomatic bacteriuria parallels that of symptomatic infection and is rare among men under 50 but common among women between 20 and 50.
- Asymptomatic bacteriuria is more common among elderly men and women, with rates as high as 40 to 50% in some studies.
- A study done by Messele Gedebou in 1980's showed that among patients with bacteruria E. coli was identified in 80% of the patients with symptomatic UTI, in Ethiopia.

Etiology

1. Etiologic agents for community acquired cases
    - *Commonest causes are E. coli (80%), S. saprophyticus(10%), Klebsiella pneumoniae (5%) and other (5%)*
    - *In acute uretheral syndrome (Sexually transmitted organisms: N. gonorrhea, Chlamydia trachomitis, Trichomonas, Candida, and herpes simplex virus may cause lower UIT)*
    - *In elderly Enterococcus fecalis may be a cause for UTI.*
    - *Bacteremia is often due to S. aureus.*

2. Hospital acquired/ catheter associated UTI
    - *E. coli (30%)*
    - *Enterococci (15%)*
    - *Pseudomonas (10%)*

- *S. aureus, yeasts, and other Enterobacteriacea*

Pathogenesis and source of infection

Routs of inoculation

- ***Urethral inoculation***: The urinary tract should be viewed as a single anatomic unit that is united by a continuous column of urine extending from the urethra to the kidney. In the vast majority of UTIs, bacteria gain access to the bladder via the urethra. Ascent of bacteria from the bladder may follow and is probably the pathway for most renal parenchymal infections. Whether bladder infection ensues depends on interacting effects of the pathogenicity of the strain, the inoculum size, and the local and systemic host defense mechanisms.

- ***Hematogenous spread:*** pyelonephritis occurs most often in debilitated patients who are either chronically ill or receiving immunosuppressive therapy. Metastatic staphylococcal or candidal infections of the kidney may follow bacteremia or fungemia, spreading from distant foci of infection in the bone, skin, vasculature, or elsewhere.

Conditions affecting pathogenesis /risk factors for UTI

1. Gender and Sexual Activity:

- The female urethra appears to be particularly prone to colonization with colonic gram-negative bacilli because of its proximity to the anus, its short length (about 4 cm), and its termination beneath the labia. Sexual intercourse causes the introduction of bacteria into the bladder and is temporally associated with the onset of cystitis; it thus appears to be important in the pathogenesis of UTIs in younger women.
- In males who are <50 years old and who have no history of heterosexual or homosexual rectal intercourse, UTI is exceedingly uncommon, and this diagnosis should be questioned in the absence of clear documentation.
- An important factor predisposing to bacteriuria in men is urethral obstruction due to prostatic hypertrophy.
- Men (and women) who are infected with HIV and who have CD4+ T cell counts of <200/μL are at increased risk of both bacteriuria and symptomatic UTI.

- Finally, lack of circumcision has been identified as a risk factor for UTI in both neonates and young men.

2. *Pregnancy*:

- Is clearly associated with altered uretheral smooth muscle function and higher incidence of asymptomatic bacteriuria and 20 to 30% of pregnant women with asymptomatic bacteriuria subsequently develop pyelonephritis.
- UTIs are detected in 2 to 8% of pregnant women. Symptomatic upper urinary tract infections, in particular, are unusually common during pregnancy.
- Bladder catheterization during or after delivery causes additional infections. Increased incidences of low-birth-weight infants, premature delivery, and newborn mortality result from UTIs during pregnancy, particularly those infections involving the upper tract.

3. *Vesicoureteral reflux:*

- Defined as reflux of urine from the bladder cavity up into the ureters and sometimes into the renal pelvis.
- Vesicoureteral reflux occurs during voiding or with elevation of pressure in the bladder.
- Vesicoureteral reflux is common among children with anatomic abnormalities of the urinary tract as well as among children with anatomically normal but infected urinary tracts. In the latter group, reflux disappears with advancing age and is probably attributable to factors other than UTI.
- Vesicoureteral reflux may promote ascending infection in several ways, including increased delivery of bacteria , increased size of inoculum , incomplete bladder emptying

4. *Obstruction*: Any impediment to the free flow of urine caused tumor, stricture, stone, or prostatic hypertrophy results in hydronephrosis. This results in urinary stasis and impairs host defense, which greatly increased the frequency of UTI.

5. *Neurogenic Bladder Dysfunction:* - Interference with the nerve supply to the bladder, as in spinal cord injury, tabes dorsalis, multiple sclerosis, diabetes, and other diseases, may be associated with UTI.

6. ***Diabetes mellitus:*** is associated with high rate of infection. Part of the risk is mediated through neurogenic bladder disturbance, and partly due to other immune disorders in diabetes.
7. ***Immune deficiency:*** congenital, acquired or drug induced immunodeficiencies are associated with increased susceptibility to infection.
8. ***Bacterial Virulence Factors****:* - Not all strains of E. coli are equally capable of infecting the intact urinary tract. Bacterial virulence factors markedly influence the likelihood that a given strain, once introduced into the bladder, will cause UTI.
9. ***Genetic Factors:*** increasing evidence suggests that host genetic factors influence susceptibility to UTI. A maternal history of UTI is more often found among women who have experienced recurrent UTIs than among controls.

Clinical presentation

Cystitis:

- Patients with cystitis usually report dysuria, frequency, urgency, and suprapubic pain.
- The urine often becomes grossly cloudy and malodorous, and it is bloody in about 30% of cases.
- If a genital lesion or a vaginal discharge is evident, then pathogens that may cause urethritis, vaginitis, or cervicitis, such as *C. trachomatis, N. gonorrhoeae, Trichomonas, Candida,* and *herpes simplex virus*, should be considered.

***Acute Pyelonephritis*:**

- Symptoms of acute pyelonephritis generally develop rapidly over a few hours or a day and include a fever, shaking chills, nausea, vomiting, and diarrhea.
- Symptoms of cystitis may or may not be present.
- Physical examination: fever, tachycardia, and generalized muscle tenderness, marked tenderness on deep pressure in one or both costovertebral angles or on deep abdominal palpation (Costvertebral angle tenderness).
- In some patients, signs and symptoms of gram-negative sepsis predominate.

***Urethritis*:**

- Approximately 30% of women with acute dysuria, frequency, and pyuria have midstream urine cultures that show either no growth or insignificant bacterial growth.

- Clinically, these women cannot always be readily distinguished from those with cystitis. In this situation, a distinction should be made between women infected with sexually transmitted pathogens, such as C. trachomatis, N. gonorrhoeae, or herpes simplex virus, and those with low-count E. coli or staphylococcal infection of the urethra and bladder.
- *Chlamydial or gonococcal* infection should be suspected in women with a gradual onset of illness, no hematuria, no suprapubic pain, and more than 7 days of symptoms.
- The additional history of a recent sex-partner change, especially if the patient's partner has recently had chlamydial or gonococcal urethritis, should heighten the suspicion of a sexually transmitted infection, as should the finding of mucopurulent cervicitis.
- Gross hematuria, suprapubic pain, an abrupt onset of illness, a duration of illness of <3 days, and a history of UTIs favor the diagnosis of *E. coli UTI.*

Catheter-Associated UTIs:

- Bacteriuria develops in at least 10 to 15% of hospitalized patients with indwelling urethral catheters. The risk of infection is about 3 to 5% per day of catheterization.
- Clinically, most catheter-associated infections cause minimal symptoms and no fever and often resolve after withdrawal of the catheter.
- Gram-negative bacteremia, which follows catheter-associated bacteriuria in 1 to 2% of cases, is the most significant recognized complication of catheter-induced UTIs.
- The catheterized urinary tract has repeatedly been demonstrated to be the most common source of gram-negative bacteremia in hospitalized patients, generally accounting for about 30% of cases.

Diagnostic work up

1. Urinalysis:

- Urinary sediment :
- Leukocytes are found in the urine : > 5 WBCs/ high power field in centrifuged urine or > 10 WBCs/ higher power field in unspun urine suggests UTI
- Microscopic bacteruria: single microorganism per oil immersion field of unspun urine is indicative of a colony growth on culture of more than 10^5 colonies /ml.

- Gram stain of urethral discharge may be help full in patients suspected of having STI associated urethritis.

2. ***Culture of the urine:*** is a definitive means for diagnosis
   - A clean catch , mid stream urine specimen should be collected
   - The growth of more than 10^5 colonies /ml in the presence of symptoms signifies infection that needs treatment
3. ***Blood:*** increased WBCs in the blood
4. ***Radiologic urologic evaluation:*** may be help full in identification of some predisposing conditions such as urolithiasis, BPH, vesicoureteral reflux

Therapy

The following principles underlie the treatment of UTIs:

1. Except in acute uncomplicated cystitis in women, a quantitative urine culture, rapid diagnostic test should be performed to confirm infection before treatment is begun.
2. Factors predisposing to infection, such as obstruction and calculi, should be identified and corrected if possible.
3. Relief of clinical symptoms does not always indicate bacteriologic cure.
4. In general, uncomplicated infections confined to the lower urinary tract respond to short courses of therapy, while upper tract infections require longer treatment
   - The anatomic location of a UTI greatly influences the success or failure of a therapeutic regimen. Bladder bacteriuria (cystitis) can usually be eliminated with nearly any antimicrobial agent to which the infecting strain is sensitive.
   - *Treatment of pyelonephritis* – Treatment decisions include whether or not to hospitalize the patient, which therapy to administer empirically, and when to order imaging studies to determine whether an infection is complicated

***Decision to hospitalize*:** Indications for admission to the hospital in acute pyelonephritis

1. Inability to maintain oral hydration or take medications
2. Concerns about patient compliance
3. Uncertainty about the diagnosis
4. Severe illness with high fevers, pain, and marked debility

Empiric antibiotic choices –

- The initial antibiotic therapy is selected on the basis of urinalysis and an understanding of epidemiology and bacteriology of the infection.

- Knowledge of the antimicrobial susceptibility profile of uropathogens in the community helps to guide therapeutic decisions.
- Ampicillin and sulfonamides should **not** be used for empiric therapy because of the high rate of resistance among causative uropathogens.
- In comparison, resistance to the fluoroquinolones and aminoglycosides is very low in uncomplicated UTIs and Aminoglycosides and fluoroquinolones achieve higher tissue levels. So these drugs are preferred for empiric treatment.
- All pregnant women should be screened for bacteriuria in the first trimester and should be treated if bacteriuria is demonstrated.

1. ***Acute Uncomplicated lower UIT in women :*** may be treated with
   - Trimethoprim –Sulfamethoxazol : 480 mg 2 tabs PO BID for 3-5 days
   - Norfloxacin 400 PO BID or Ciprofloxacin 500 mg PO BID for 5-7 days
2. ***Acute uncomplicated pyelonephritis in women*** : *E. coli*, *P. mirabilis*, *S. saprophyticus* are the common causes
   - Norfloxacin 400 PO BID or Ciprofloxacin 500 mg PO BID for 7-14 days or
   - Single dose of Ceftriaxon 1gm or Gentamicin 80 mg IV followed by Trimethoprim –Sulfamethoxazol : 480 mg 2 tabs PO BID for 14 days
3. ***Complicated UTI in men and women:*** *E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas*, *Serratia*, enterococci, staphylococci are the common etiologies.
   - Mild to moderate illness, no nausea or vomiting: outpatient therapy
   - Norfloxacin 400 PO BID or Ciprofloxacin 500 mg PO BID for 10-14 days or
4. ***Severe illness or possible urosepsis:*** hospitalization is required***.***
   - Ceftriaxone 1gm IV daily or BID
   - Gentamicine 80 mg IV TID
   - Ampicillin 1gm IV QID and then 500 mg IV QID
   - IV quinolones such as Ciprofloxacin 200-400 mg IV BID can also be used if available
   - If enterococcus is suspected based upon the Gram stain, ampicillin (1 to 2 g IV Q6h) plus gentamicin (1.0 mg/kg IV Q8h or adjusted for renal function).

Note: IV medication should be changed to PO as soon as the patient became afebrile and then give PO TMP-SMX or Ciprofloxacin or Norfloxacin for 10- 21 days.

Parenteral therapy – For hospitalized patients, aminoglycosides (3 to 5 mg/kg) given once daily are cost effective , associated with low toxicity when used for short durations, and

may provide a therapeutic advantage compared with beta lactams, because of their marked and sustained concentration in renal tissue .

Urologic evaluation.

- Routine urologic investigation of young healthy women with acute uncomplicated pyelonephritis is generally not recommended.
- Urologic consultation and evaluation of the upper urinary tract with an ultrasound should be considered if the patient remains febrile or has not shown signs of demonstrable clinical improvement after 72 hours of treatment to rule out the presence of obstruction, renal or perinephric abscesses, or other complications of pyelonephritis.
- It is reasonable to perform a urologic evaluation, starting with renal ultrasound to rule out nephrolithiasis or obstructive uropathy, after two recurrences of pyelonephritis or if any complicating factor is identified.

Prognosis

- In patients with uncomplicated cystitis or pyelonephritis, treatment ordinarily results in complete resolution of symptoms. When repeated episodes of cystitis occur, they are nearly always reinfections, not relapses.
- Acute uncomplicated pyelonephritis in adults rarely progresses to renal functional impairment and chronic renal disease. Repeated upper tract infections often represent relapse rather than reinfection, and a vigorous search for renal calculi or an underlying urologic abnormality should be undertaken. If neither is found, 6 weeks of chemotherapy may be useful in eradicating an unresolved focus of infection.
- Repeated symptomatic UTIs in children and in adults with obstructive uropathy, neurogenic bladder, structural renal disease, or diabetes may progress to chronic renal disease with unusual frequency. Asymptomatic bacteriuria in these groups as well as in adults without urologic disease or obstruction predisposes to increased numbers of episodes of symptomatic infection but does not result in renal impairment in most instances.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Urinary tract infection and pyelonephritis , pages 1715-1721.

2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Urinary tract infection, Pages 284-285.

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CHAPTER FIVE
DISEASES OF THE GASTRO INTESTINAL SYSTEM

1. Approach to a patient with gastrointestinal disorder

Learning objectives: at the end of this unit the student will be able to

1. *List the symptoms of gastrointestinal diseases*
2. *Characterize each symptom of gastrointestinal diseases*
3. *Describe the investigations for gastrointestinal diseases*
4. *Outline the steps in paracentesis*
5. *Describe the difference between exudates and transudates and their clinical use*
6. *List the different radiological and endoscopic investigations and their clinical use*

Patients with gastrointestinal disorders may present with a variety of symptoms that are specific to the gastrointestinal tract and/or general systemic symptoms. Disorders of the gastrointestinal tract also give a variety of signs.

Common symptoms include:

- Abdominal pain, abdominal distension
- Dyspepsia
- Diarrhea or constipation
- Gastrointestinal bleeding
- Jaundice
- Change in weight and change in appetite
- Nausea vomiting
- Change in stool color

- During history taking, detailed analysis of the above symptoms should be done, and history of medications should also be elicited.
- The usual techniques and steps of physical examination of the gastrointestinal system should be followed, that include: inspection, auscultation, percussion, and palpation

Diagnostic work up of patients with gastrointestinal diseases

1) ***Stool microscopy* for i**ntestinal parasite; ova, cyst or trophozoites, pus cells and red blood cells
2) ***Stool culture*** - indicated in certain cases of infectious diarrhea
3) ***Chemical analysis of stool* t**est for fecal fat and occult blood
4) ***Aspiration of peritoneal fluid (abdominal paracentesis) could be:-***
   - **Diagnostic** – for evaluation of clinically evident ascites
   - **Therapeutic** – to remove fluid in case of refractory ascites with respiratory embarrassment.

   Technique
   - Empty the urinary bladder
   - Patient lying flat or slightly probed up
   - Give local anesthetics if available
   - Site of aspiration is the right iliac fossa, a little outside the midpoint of a line joining the umbilicus to anterior superior iliac spine.
   - For diagnostic purpose 10cc syringe may be used
   - For therapeutic purpose trocar and flanged cannula are used. If this is not available intravenous set with needle may be used.

The fluid is analyzed biochemically, bacteriologically, cytologically and physically.

- Biochemical – protein, glucose, Lactate dehydrogenase (LDH)
- Bacteriology – Gram staining, AFB staining
- Culture
- Cytology – cell count and differential; look for malignant cells
- Physical – color, specific gravity

Based on the above analysis, ascites is classified into two: exudative and transudative, and the main differences are outlined below:

Table V-1-1, Main differences between exudative and transudative ascetic fluids

	Exudative	***Transudative***
Specific gravity	> 1.018	< 1.018
Protein	> 2.5 gm/dl	< 2.5 gm/dl
Serum ascetic albumin gradient)	< 1.1	> 1.1
Causes	Bacterial peritonitis TB peritonitis Malignancy	CHF Cirrhosis Nephrotic syndrome

5) Radiology of the gastrointestinal tract

- **Plain x-ray** – no contrast is used and can be taken erect (to see for air fluid level) or supine.
- **Contrast x-rays** – barium is used to outline the lumen of the gastrointestinal tract. Different terminologies are used to describe barium studies of the different parts of the gastrointestinal tract:
    - For esophagus - Barium swallow.
    - For stomach - Barium meal.
    - For intestine - Barium meal and follow through.
    - For Rectum - Barium enema
- **Indications for x-ray of the GI tract include**
    - Intestinal obstruction (plain films)
    - Dysphagia
    - Peptic ulcer disease
    - Inflammatory bowel disease

6) **Endoscopy** is visualization of the lumen of the GI tract with endoscope. Endoscopes are of two types depending their flexibility

- **Rigid** used for removal of foreign body
- **Fibro-optic** is flexible and used for visualization of the GI tract

Depending on the structures to be visualized endoscopes can be divided into

A) Upper GI endoscopy:-

- It is used to visualize structures up to the second part of the duodenum.

- It can be used for diagnostic and therapeutic purposes (to stop bleeding varices, ulcers, or to dilate esophageal strictures)

B) Lower GI endoscopy: there are three different types of lower GI endoscopies, to visualize the different parts of the large intestine:

- **Colonoscopy**: for diagnosis and management of colonic polyps and ulcers
- **Sigmoidoscopy**: to visualize the sigmoid colon.
- **Proctoscopy**: to visualize the rectum and anus.

Diagnostic work up of patients with diseases of hepatobiliary system

1. Biochemical tests:

- **Tests for the detoxification capacity of the liver :**
  - Serum ammonia level
  - Serum bilirubin, urine bilirubin level
- **Tests for synthetic function of the liver:**
  - Serum albumin level
  - Prothrombin time
- **Tests indicating hepatocellular damage**
  - Transaminases (serum glutamic oxalate transferase (SGOT) and serum glutamic pyruvate transferase (SGPT))
- ***Tests which show cholestasis***
  - Alkaline phosphatase
  - (Direct) bilirubin level.

2. ***Ultrasound*** is a noninvasive procedure that may be help full in diagnosing the following diseases:

- Cirrhosis
- Metastasis
- Fluid filled lesions – cysts, abscess
- Cholelithiasis

3. ***Biopsy –*** can be done in two forms

- Open biopsy is done during laparatomy and allows to take adequate tissue samples

- Needle biopsy is done percutaneously

4. ***Cholangiography:*** is contrast study of the biliary tree. The contrast can be given orally, percutaneously, intravenously, or by using endoscope; the last is known as Endoscopic Retrograde Cholangiopancreaticography (ERCP)

References:

2) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Approach to patients with Gastrointestinal diseases , pages 1725-1729.

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2. Gastritis and peptic ulcer diseases

Objectives: at the end of this unit the student will be able to:-

1. *Define gastritis and peptic ulcer diseases (PUD).*
2. *List the etiologies of gastritis and PUD.*
3. *Describe the epidemiology of PUD.*
4. *Explain the pathogenesis gastritis and PUD.*
5. *Describe the clinical features of gastritis and PUD.*
6. *List the common complications gastritis and PUD.*
7. *Describe the most commonly used methods for the diagnosis of gastritis and PUD.*
8. *Make an accurate diagnosis of gastritis and PUD.*
9. *Treat gastritis and PUD at the primary care level with appropriate drugs.*
10. *Refer those presenting with complications of gastritis and PUD to hospitals.*

2.1 Gastritis

- Gastritis refers to histologically confirmed inflammation of the gastric mucosa. It is not synonymous with dyspepsia or gastric erythema seen during endoscopy. It is classified into:

Acute gastritis

- Commonly caused by: *Helicobacter pylori*.
- Other causes include :
  - Drugs like ASA, **NSAID**,
  - Alcohol in high doses,
  - Severe stress, and
  - Other infections such as viruses (CMV, Herpes simplex), mycobacterium, and syphilis.
- Patients are usually asymptomatic but at times they may present with sudden onset of epigastric pain, with neutrophilic infiltration, edema and hyperemia of the gastric mucosa.

- If not treated, *H. pylori* gastritis may progress to one of the chronic gastritis. No specific treatment of acute gastritis is indicated. Removal of the offending agents may be adequate.

Chronic gastritis

- Defined as a histological demonstration of lymphocytic and plasma cell infiltration of gastric mucosa.
- **Course:** Superficial gastritis is followed by atrophic gastritis (characterized by distortion and destruction of gastric glands) progressing to gastric atrophy (with loss of gastric glands), which then undergo intestinal metaplasia (replacement of gastric mucosal cells by intestinal epithelial cells) and finally progressing to gastric carcinoma.

Chronic gastritis is classified into two:

- **Type A gastritis (chronic fundal gastritis)**
  - The inflammation is limited to gastric fundus and body with antral sparing.
  - Associated with pernicious anemia, with circulating autoantibodies to parietal cells, which is why it is also known as autoimmune gastritis.
- **Type B- gastritis (chronic antral gastritis)**
  - It is more common than type gastritis.
  - It commonly involves the antrum and mostly associated with *H. pylori* infection. However, the inflammation may progress to involve the gastric fundus and body causing pangastritis usually after 15 - 20 years.
  - Histology improves with eradication of *H. pylori.*

Treatment of chronic gastritis: is aimed at controlling the sequellae, not the inflammatory process.

- Lifelong parenteral Vitamin-B_{12} is recommended for patients with pernicious anemia.
- There is no need to treat *H. pylori*, unless there is ulcer or MALT Lymphoma.

2.2 Peptic ulcer diseases

Definition: An ulcer is a break in the mucosal surface, bigger than 5mm in size with depth to sub- mucosa.

- Peptic ulcer is caused by discrete tissue destruction caused by acid and pepsin.
- Ulcers occur most commonly in the stomach (GU) and proximal duodenum (DU), and less commonly in the esophagus, and rarely on the other portions of small intestine.

Incidence:

- Duodenal ulcers occur more frequently than gastric ulcers. This is probably due to the likelihood of gastric ulcers being silent and presenting only after complications. Autopsy studies suggest similar incidence of gastric ulcers and duodenal ulcers.
- Peptic ulcer disease occurs more commonly in males than females.
- Gastric ulcers occur later in life than duodenal ulcers (peak is in the sixth decade).
- About 90 -100% of duodenal ulcers and 75 - 85% of gastric ulcers are associated with *H. pylori* infection.
- About 15 - 20% of patients have both gastric and duodenal ulcers.
- Patients with gastric ulcers have a 33% chance of developing subsequent duodenal ulcers.

The most important risk factors are:

1. Helicobacter pylori infection:

- *H. pylori* is a gram negative microaerophilic rod bacteria found attached to gastric epithelium, without invading the gastric epithelium.
- The bacterium produces lots of factors, which enable its existence in the acidic environment that include:
    - Urease: which splits urea to CO_2 and ammonia, and alkalinize the acidic environment
    - Catalase, adhesins, lipase, platelet activating factor, etc.
- The prevalence of *H. pylori* infection varies throughout the world and depends to a great extent on the overall standard of living.
- In developing countries 80% of the population may be infected by age 20.
- Transmission of *H. pylori* occurs from person to person following an oral-oral or fecal-oral route.

Pathophysiology:

- *H. pylori* infection is virtually associated with chronic active gastritis, but only 10 - 15% of the infected individuals develop frank peptic ulcerations. The basis for this difference is unknown. The end results are dependent upon the interplay between bacterial and host factors.
- *H. pylori* infection is present in 90 - 100% of duodenal ulcers and 75 - 85% of gastric ulcers.
- The end results of *H. pylori* infection are:-
    - Gastritis
    - Mucosa associated lymphoid tissue Lymphoma (MALT lymphoma)
    - peptic ulcer diseases
    - Gastric cancer
    -

2. Non-steroidal anti inflammatory drugs

- These are among the commonly used over-the-counter and prescription drugs.
- The spectrum of morbidity ranges from nausea and dyspepsia (50 - 60%) to serious gastrointestinal complications, such as frank peptic ulceration complicated by perforations or bleeding in as many as 3 - 4% of users per year.
- These drugs inhibit prostaglandin synthesis, which maintains gastro- duodenal mucosal integrity and repair.
- Gastric ulcers occur at somewhat higher frequency than duodenal ulcers.

3. Miscellaneous factors

- ***Cigarette smoking*** - Higher incidence of peptic ulcer disease and complications in smokers, with delayed ulcer healing.
- ***Generic factors***, ***personality, and diet*** may be associated with PUD; however the mechanisms are not yet established.
- Corticosteroids alone do not predispose to ulcers; but they increase the risk of ulcer development if given with NSAIDS.

Pathophysiology of Ulcer Diseases

Peptic ulcers develop as a result of an imbalance between protective mucosal defensive factors and aggressive factors

- ***Defensive factors include***

- Prostaglandins,
- Mucus
- Bicarbonates
- Mucosal blood flow

- Aggressive factors
  - Pepsin
  - Hydrochloric acid.

Whereas acid-peptic injury is necessary for ulcer to develop, acid secretion is normal in almost all patients with gastric ulcers and increased in approximately a third of patients with duodenal ulcers.

Clinical presentations

- Manifestations are dependent on ulcer location and patient age.
- Course is usually chronic and recurrent.
- Pain is the most common symptom, and described as burning, gnawing or felt as hunger, often localized to epigastrium and relieved by food or antacids

Gastric ulcer

- Symptoms often do not follow a consistent pattern, especially when ulcer is located in pyloric channel, where symptoms of obstruction may predominate (bloating, nausea, vomiting due to edema and scarring).

Duodenal ulcer

- Pain tends to be consistent, usually absent when patient wakes up but appears in midmorning, and relieved by food but recurs again 2 - 3 hours after a meal.
- Pain may be severe enough to awaken patient at night.

Table V-2-1. Some differences in the clinical manifestations between DU and GU

	Duodenal ulcer	***Gastric ulcer***
Age	Uncommon before age 15 yrs	May develop in children as young as 5 yrs, but peak incidence is later than DU.
Relation of pain to food/antacids	Pain is relieved by food or antacids	Pain aggravated by ingestion of food
Relation of pain to food timing	The pain characteristically comes 90 minutes to 3 hr after ingestion of food (hunger pain)	The pain comes within 30 minutes of ingestion of food
Nausea and vomiting	Not common	Common
Weight loss	Uncommon	Common because of fear to eat
Perforation	more common	Less common
Bleeding	Less common	more common

Change in the character of pain may herald development of complications:

- Duodenal ulcer pain that becomes constant, is no longer relieved by food or antacids, or radiates to the back or to either upper quadrant, may signal penetration of the ulcer to the pancreas.
- Duodenal ulcer pain accentuated rather than relieved by food, and/or accompanied by vomiting often indicates gastric outlet obstruction (G.O.O).
- Abrupt, severe or generalized abdominal pain is characteristic of free ulcer perforation into the peritoneal cavity.

Physical finding

- Epigastric tenderness is most frequent finding.
- Signs of peritonitis may be found in ulcer perforation.
- Succussion splash is often detected in gastric outlet obstruction.

Complications of PUD: All patients with the following complications need special care at referral hospitals

- ***Haemorrhage***
  - Is the most common complication of PUD, and patients present with hematemesis, passage of tarry stools, weakness, hypotension, syncope, thirst and sweating resulting from associated blood loss.
  - Immediate treatment can be given via endoscopy (electrocautery, injection of alcohol/sclerosant etc.) or surgery.
- ***Penetration (confined perforation)***
  - Is entering of adjacent confined space (e.g. lesser sac) or organ (e.g. pancreas, liver).
  - Adhesions prevent leakage into peritoneal cavity.
  - Radiographic evaluation with contrast study is usually needed to confirm the diagnosis.
  - When medical therapy does not produce healing, surgery is recommended.
- ***Free perforation***
  - Usually presents as acute abdomen with sudden, intense, steady epigastric pain.
  - Diagnosis is confirmed with upright or lateral decubitus x-ray of abdomen.

- **Gastric outlet obstruction (GOO)**
  - May be caused by scarring, spasm, or inflammation.
  - Symptoms include recurrent large volume vomiting, persistent bloating, fullness after eating, loss of appetite; weight loss, dehydration and alkalosis due to prolonged vomiting.
  - Succussion splash for over 6 hrs after a meal, gastric aspiration or x - rays may help in the diagnosis.
  - Treat such patients with nasogastric tube aspiration and acid suppression if causes are temporary. But if the pyloric canal scarred, do endoscopic pyloric balloon dilatation or surgical relief of obstruction.
- ***Stomach cancer***
  - Is intestinal type adenocarcinoma of gastric body and antrum and commonly associated with *H. pylori* infection.

- Moreover, the incidence of MALT lymphoma (MALT=mucosa-associated lymphatic tissue) is increased in PUD.
- Treating *H. pylori* might cure lymphoma, but chemotherapy or radical surgery must be used when such treatment fails to cure the tumour.
- For adenocarcinoma, surgery is always treatment of choice

Diagnosis of PUD

1) ***Barium examination of the upper gastrointestinal tract***: sensitivity of this investigation to detect ulcers ranges from 70 – 90%
2) ***Endoscopy*****:** is most sensitive and specific method for the diagnosis of PUD.

Advantages

a) Direct visualization and photographic documentation of the ulcer is possible.
b) Permits mucosal biopsy for detection of H. pylori infection.
c) Provides baseline reference for the assessment of ulcer healing.

3) ***Tests for H. pylori*** **T**here are two categories of tests for the diagnosis of this bacterium:

i) Invasive tests (endoscopy required)

- Rapid urease test
- Histology
- Culture

ii) Non invasive tests

- Urea breath test - simple, rapid; useful for early follow up, false negative with recent therapy.
- Serology – inexpensive, convenient, not useful for early follow-up

Treatment

Objectives of treatment:

- Relief of symptoms (pain, dyspepsia)
- Eradication of *H. pylori* to prevent recurrence
- Promote ulcer healing

Medical treatment

I. Treatment of H. pylori (see table VII-2-2)

Indications: the following diseases with documented H. pylori infection

- PUD
- MALT lymphoma

- No single agent is effective for eradication of *H. pylori*; hence a combination of multiple drugs is essential. Proton pump inhibitors (omeprazole) are added to antibiotics or H_2 blockers (e.g. Ranitidine) can be used alternatively.

Table *V-2-2* Regimens recommended for eradication of H. pylori infection

Triple therapy	**Dose**	**Duration**
Bismuth subsalicylate plus	2 tabs QID	2 weeks
Metronidazole plus	250 mg QID	
Tetracycline	500 mg QID	
Omeperazole plus	20 mg, BID	2 weeks
Chlarithromycin plus	250 or 500mg BID	
Metronidazole or amoxicillin	500 mg BID/1 gm BID	
Quadruple therapy		
Omeperazole +	20 mg, BID	2 weeks
Bismuth subsalicylate +	2 tabs QID	
Metronidazole +	250 mg QID	
Tetracycline	500 mg QID	

II. Acid Neutralizing/Inhibitory Drugs

A) Antacids

- Are the most frequently used drugs before the advent of antihistamines (H_2 -blockers). They are now rarely, if ever, used as the primary therapeutic agent, however are often used by patients for symptomatic relief of dyspepsia.
- A combination of magnesium hydroxide and aluminum hydroxide (marketed as Maalox or other brands) are widely used at a dose of 15 -30 ml at 1 hour and 3 hours after each meal and at bedtime.

B) H_2 receptor antagonists

- Include cimetidine, famotidine, ranitidine and nizatidine.
- Cimetidine is the most commonly used drug. The dose is 800 mg at bedtime or 400mg twice a day for 4 - 6 weeks.
- Ranitidine is used at a dose of 150 mg orally twice a day or 300mg at bedtime for 4 – 6 wks.

C) Proton pump inhibitors

- They inhibit the H^+-pump, which is important for synthesis of hydrochloric acid.
- Omeperazole: 20mg orally daily for 4 - 8 weeks.
- When these drugs are used for anti- *H. pylori* treatment, it has direct antimicrobial effect on the organism.

D) Dietary advice

- There is no specific diet recommended for patients with peptic ulcer disease.
- Patients are generally advised to avoid smoking, coffee, and foods that cause or aggravate their symptoms.

***Surgical treatment* is indicated for:**

- ***Perforation:*** immediate surgery is recommended for acute perforation. If this is not possible, admit the patient to ICU and put on continuous nasogastric suction and broad-spectrum antibiotics.
- ***Obstruction not responding to medical therapy***
- ***Uncontrolled/recurrent bleeding***
- ***Suspected malignancy***
- ***Symptoms refractory to medical management***

N.B. For the types of surgical procedures and their complications, please refer Surgical textbooks.

Dyspepsia

- Is the classic symptom of PUD and is defined as pain centered in the upper abdomen or discomfort characterized by fullness, bloating, distension or nausea.
- It's a common clinical problem and may be seen in 25 - 40% of adults.
- Only 15 - 25% patients with dyspepsia are found to have either gastric or duodenal ulcers.
- Other causes include:
  - Gastroesophageal reflux disease

- Gastric cancer
- Gastroparesis
- Gastritis

- In up to 60% of dyspeptic patients no cause is identified (**Functional or non ulcer dyspepsia**) - a condition most likely related to an abnormal perception of events in the stomach caused by afferent visceral hypersensitivity.

Non gastritis mucosal Injury

1. NSAIDS

- Acute ingestion: increases mucosal permeability and back diffusion of H^+ leading to hyperemia, sub epithelial hemorrhage and superficial erosions.
- Chronic ingestion: inhibition of gastro duodenal mucosal prostaglandin synthesis leading to decreased mucus and bicarbonate production and mucosal blood flow finally resulting in frank ulceration may occur.

2. Stress Related mucosal Damage

- Mucosal ischemia caused by decreased blood flow (from shock, Catecholamine release) impairs mucosal resistance to acid back diffusion. Hyperemia of the mucosa evolves & erosions and then frank ulceration in the stomach and duodenum that go on to bleeding.

Clinical features

- May be absent
- Epigastric pain
- Hemorrhage (hematemesis, melena)

Diagnosis – History of drug ingestion

- Endoscopy

Treatment:

- Removal of offending agent.
- Antacids, H2-blokcer and surface acting agents (Sucralfate) are helpful.
- In patients with hemorrhage – Volume replacement and endoscopic control of the bleeding.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Peptic ulcer diseases and related disorders, pages 1746-1762.

2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Peptic ulcer diseases, pages 210-215.

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3. Malabsorption syndromes

Learning Objectives: at the end of this chapter the student will be able to

1. *Define malabsorption syndromes*
2. *List the etiologies of malabsorption syndromes*
3. *Explain the mechanisms of malabsorption syndromes*
4. *Describe the clinical features of malabsorption syndromes*
5. *List the common nutritional complications malabsorption syndromes.*
6. *Make a diagnosis of malabsorption syndrome*
7. *Refer the patient to hospitals for better diagnosis and treatment*

Definition: *Syndromes resulting from impaired absorption of one or more dietary nutrients from the small bowel.*

- Many diseases or their consequences can cause malabsorption.
- The mechanism may be direct impairment of absorption or abnormalities of digestion that finally leads to impaired absorption.
- Malabsorption may occur for specific nutrients such as carbohydrates, fats, or micronutrients or may affect many nutrients at the same time.

Etiologies

1) ***Maldigestion:*** refers to a defect either in the intraluminla hydrolysis of triglycerides, or in micelle formation , which results from the following conditions

- ***a) Pancreatic insufficiency*** due to chronic pancreatitis , pancreatic carcinoma
- ***b) Deficiency of conjugated bile salts*** due to cholestatic or obstructive liver diseases
- ***c)*** Bile salt deconjugation due to bacterial overgrowth in blind loop (after Billroth-II gastrectomy) or jejuna diverticulitis
- ***d) Inadequate mixing of gastric contents*** with bile salts and pancreatic enzymes as a result of previous gastric surgery

2) ***Intrinsic bowl diseases*** (damage to the absorptive surface of the intestine)

- ***a) Celiac disease*** causing flattening of the intestinal villa and inflammatory cell infiltration.
- ***b) Whipple's diseases:*** is a systemic disease that may cause intestinal mucosal damage and lymphatic obstruction.

c) ***Collagenous sprue***: deposition of collagen substance in the lamina propia of the intestine

d) ***Non granulomatous ulcerative ileojejunitis*** a rare condition of unknown etiology characterized by fever, weight loss and features of absorption.

e) ***Eosinophilic gastroenteritis:*** characterized by peripheral eosipnophilia, and infiltration of the wall of the stomach, small intestine or colon by eosinophils. Many patients present with specific food allergy.

f) ***Amylodosis :*** amyloid infiltration of the submucosa of the small intestine

g) ***Crohn's diseases :*** an inflammatory bowel diseases which may cause mucosal damage

3) Inadequate absorptive surface: from extensive small bowel resection. Resection of 50 % of small intestine is well tolerated, if the remaining bowel is normal.

4) Lymphatic obstruction

a) Intestinal lymphangiectasia

b) Intestinal lymphoma

5) Multiple defects

a) **After gastrectomy**: which may result in poor mixing of gastric contents with pancreatic enzymes and stasis in the afferent loops with bacterial overgrowth (as in Billroth II gastrectomy) can cause malabsorption.

b) ***Radiation enteritis***: interferes with the blood supply of the intestine. Bacterial overgrowth may occur secondary to radiation stricture , lymphatic obstruction may occur due to edema or fibrosis

c) **Diabetes mellitus**: alter gut motility from diabetic neuropathy, bacterial overgrowth and exocrine pancreatic insufficiency may lead to malabsorption.

6) Other causes

a) ***Infections :*** viral , bacterial or parasitic infections may cause malabsorption

i) ***In HIV infected patients*** malabsorption may be caused by Cryptosporidiosis , Isosporiosis or intestinal mucosal atrophy due to HIV virus itself (HIV enteropathy)

ii) ***Tropical sprue:*** endemic malabsorption disorder occurring in the tropics. It is believed to have an infectious cause.

iii) ***Parasitic cause of malabsorption***: include Hookworm, tapeworm and strolgyloidiasis.

b) ***Hypoparathyroidism***

c) ***Drugs:*** neomycin, kanamycine may cause malabsorption. Phenytoin causes a selective folic acid malabsorption

Clinical features

Signs and symptoms

- Symptoms of malabsorption are caused either by the effects of osmotically active substances within the gastrointestinal tract or the resulting nutritional deficiencies.
- Patients may present with some or all of the following clinical manifestations.

General symptoms:

- ***Steatorrhea:*** passage of abnormal stools, which are greasy soft , bulky , and foul smelling and may float in the toilet because of their increased gas content : a film of greasy or oil droplets may be seen on the surface of the water . This is often associated with abdominal distension, bloating, or discomfort and flatulence resulting from increased intestinal bulk and gas production
- ***Weight loss:*** which may be severe and involve marked muscle wasting.

Secondary nutritional deficiencies:

- Deficiency of iron, folic acid, or B12 leading to anaemia
- Calcium deficiency (common) partly due to lack of vitamin D causing rickets, osteomalacia , paresthesia***,*** tetany and carpopedal spasms.
- Thiamine (vitamin B_1) and B_{12} deficiency may cause neuropathy,
- Malabsorption of vitamin K (mainly fat-soluble) can lead to hypoprothrombinemia with bruising and a bleeding tendency.
- Severe riboflavin (vitamin B_2) deficiency may cause a sore tongue and angular stomatitis,
- Vitamin A, C, and niacin deficiencies seldom cause clinical problems.
- Protein malabsorption may lead to hypoproteinemic edema, usually of the lower limbs.
- Dehydration, potassium loss, and muscle weakness can follow profuse diarrhoea.
- Secondary endocrine deficiencies may result from malnutrition.

Some causes of malabsorption may have distinct clinical features:

- Lactase deficiency manifests with explosive diarrhoea, abdominal bloating and gas after milk ingestion
- Pancreatic lipase deficiency: greasy stools with undigested dietary fat (triglycerides)
- Dermatitis herpetiformis is often associated with a mild degree of celiac-like enteropathy
- Biliary cirrhosis and pancreatic cancer may cause jaundice
- Mesenteric ischemia may cause abdominal angina
- Chronic pancreatitis may cause boring central abdominal pain
- Patients with Zollinger-Ellison syndrome frequently manifest with severe persistent ulcerative dyspepsia.

Diagnostic workup

- Symptoms and signs may point to the diagnostic impression of malabsorption.
- Any combination of weight loss, diarrhoea, and anaemia should raise the suspicion of malabsorption.
- However, laboratory studies are essential to confirm the diagnosis

Common laboratory tests:

1) **Direct measurement of faecal fat:** 3 - 4 days stool collection is required for this measurement. Faecal fat over 6 g/day is abnormal.
2) **Stool inspection, microscopic examination:** look for undigested food fragments, and do direct microscopy for ova and parasites, and Sudan III staining for the presence of grease/fat in the stool.
3) **Absorption tests help to define the site of the lesion; D-xylose absorption test is specific for proximal small-bowel (jejunal) absorption.** Five grams of D-Xylose is given orally to the fasting patient, and urine is collected for the next 5 hours. Smaller than 1.2 grams of D-xylose in the 5-hours urine collection is considered abnormal.
4) **Iron malabsorption:** low serum ferritin and serum iron levels with adequate diet and lack of blood loss indicates iron malabsorption. Diminished iron storage on bone marrow examination may also be found.
5) **Folic acid absorption:** is suggested by low serum or RBC folate level with adequate diet and little alcohol intake.
6) **Schilling test is used to diagnose Vit B-12 malabsorption.**

7) **Abdominal X-rays:** upper GI series with small-bowel follow-through may be helpful. Plain abdominal x-ray may show pancreatic calcification as a sign of chronic pancreatitis.
8) **Small-bowel biopsy** can be taken during endoscopy to show mucosal changes.

Treatment

- Is individualised according to underlying disease.
- However, if the underlying cause is not treatable as in short bowel syndrome, adequate substitution of missing nutrients must be ensured and diet adjusted appropriately.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Disorders of absorption , pages 1763-1775.

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4. Pancreatic diseases

Learning objectives: at the end of this unit the student will be able to

1. *Define acute and chronic pancreatitis*
2. *List the etiologies of acute and chronic pancreatitis*
3. *Explain the mechanisms of acute and chronic pancreatitis*
4. *Describe the clinical features of acute and chronic pancreatitis*
5. *List the common complications acute and chronic pancreatitis*
6. *Make a diagnosis of acute and chronic pancreatitis &*
7. *Refer patients to hospitals for better diagnosis and treatment*

4.1. Acute Pancreatitis

Etiology:

1) Biliary tract disease especially stones
2) Alcoholism
3) Drugs (furosemide, valproic acid, azathioprine, sulfasalazine)
4) Infection (e.g. mumps)
5) Hypertriglyceridemia
6) Structural abnormalities of pancreatic duct (stricture, cancer, pancreas divisum)
7) Abnormalities of common bile duct and ampullary region
8) Surgery of stomach, biliary tract
9) Vascular disease
10) Trauma
11) Hyperparathyroidism, hypercalcemia

Signs and symptoms:

- Fever
- Severe abdominal pain radiating to the back; sudden in biliary pancreatitis, developing over weeks in alcoholism. Pain is steady, boring, persistent, relieved by leaning forward, and accentuated by coughing, movement and deep breathing.
- Abdominal tenderness with muscular rigidity, and sometimes board like abdomen

- Hypoactive bowel sounds
- Nausea, vomiting
- Tachycardia, tachypnia
- Jaundice may be present
- Lung examination may reveal limited diaphragmatic excursions and evidence of atelectasis

Complications:

- Early death may be due to cardiovascular instability or respiratory failure; later death due to pancreatic or pseudocyst infection.
- Pancreatic infection of devitalized retroperitoneal tissue with sepsis
- Pancreatic pseudocyst may be secondarily infected, bleed or rupture

Diagnosis:

- **Increased serum amylase, lipase**
- **WBC**: usually between 12,000 to 20,000/mm^3
- **Hematocrit** may be as high as 50-55 % due to third-space losses.
- **Hyperglycaemia**
- **Serum calcium** is decreased
- **Bilirubin** may be increased
- **X-rays of the abdomen (Supine and upright plain x-rays); Chest x-ray**
- **Ultrasound of the abdomen (if available CT)**

Differential diagnosis: the following diseases can mimic acute pancreatitis

- Perforated gastric or duodenal ulcer
- Mesenteric infarction
- Strangulating intestinal obstruction
- Ectopic pregnancy
- Dissecting aneurysm
- Biliary colic
- Appendicitis
- Diverticulitis
- Inferior wall myocardial infarction
- Haematoma of abdominal muscles or spleen.

Prognosis

Ranson's 11 prognostic signs help estimate the prognosis of acute pancreatitis.

- **Five signs can be documented at admission:**
  - Age more than 55 yr
  - Serum glucose over 200 mg/dl (> 11.1 mmol/L),
  - Serum LDH over 350 IU/L
  - AST over 250 units/L and
  - WBC count over 16,000/µL.
- **The development of the following within 48 h after admission indicates worsening prognosis:**
  - **Hct** drop by more than 10%
  - BUN rise greater than 5 mg/dl (> 1.8 mmol Urea/L)
  - Serum Ca less than 8 mg/dl (< 2 mmol/L)
  - Arterial Po_2 less than 60 mm Hg
  - Base deficit over 4 meq/l
  - Estimated fluid sequestration more than 6 L
- **Mortality increases with the number of positive signs:**
  - If fewer than three signs are positive, the mortality rate is less than 5%;
  - If three or four signs are positive, mortality is between 15 to 20%.
  - The presence of 7 – 8 of these criteria is associated with 100% mortality.
- Acute pancreatitis associated with necrosis and haemorrhage has a mortality rate of about 10 to 50%. This diagnosis is suggested by
  - A progressive decrease in Hct,
  - The presence of hemorrhagic fluid within ascites,
  - The reduction of serum Ca^{++} level,
  - The presence of **Grey Turner's** and/or **Cullen's sign** (indicating extravasations of hemorrhagic exudates to the flanks or umbilical region, respectively).

Treatment

Mild oedematous pancreatitis:

- Keep patient NPO (nothing per os) until manifestations of acute inflammation subside
- Give sufficient intravenous fluids
- Insert nasogastric tube.

Severe acute pancreatitis:

- Refer to hospitals for admission to intensive care unit
- Vital signs and urine output are monitored at least every 1 hr
- Accurate metabolic flow sheet which should be checked every 8 hrs.
  - Arterial blood gases are determined as necessary
  - Hct, glucose, electrolytes (Ca, Mg), CBC, platelet count, coagulation parameters, total protein with albumin, BUN, creatinine, amylase, and lipase studies performed daily.
  - Keep patient NPO with NG tube insertion
  - Give H_2 receptor blockers IV
  - Fluids may be given up to 6 - 8 L/d.
  - Give oxygen as needed
  - Severe pain should be treated with Pethidine 50 to 100 mg IM every 4 to 6 hrs and as needed in patients with normal renal function (morphine causes the sphincter of Oddi to contract and should be avoided).
  - Treat hyperglycaemia if over 250 mg/dl.
  - If symptoms of calcium depletion appear give calcium gluconate 10 - 20 ml IV in 1 liter of replacement fluid.

Surgery is indicated for

- Trauma
- Uncontrolled biliary sepsis
- Inability to distinguish acute pancreatitis from other causes of acute abdomen
- To drain a pseudocyst that is expanding rapidly, secondarily infected, or associated with bleeding or impending rupture.

4.2. Chronic pancreatitis

Etiology:

- Alcoholism : 70 -80% of chronic pancreatitis is associated with alcoholism
- Idiopathic
- Hereditary
- Microlithiasis
- Hyperparathyroidism
- Obstruction of the main pancreatic duct due to stenosis, stones, or cancer

***Signs and symptoms*:**

- Persistent or recurrent epigastric or left upper abdominal pain, nausea, vomiting, anorexia, constipation, flatulence and weight loss are common.
- In advanced disease, patients may develop steatorrhea, recurrent acute attacks of pain which become more constant later and insulin secretion is diminished with impaired glucose tolerance.

Diagnosis:

- **Laboratory tests** are frequently normal, but inflammation markers may be minimally elevated.
- **Plain abdominal x-ray** may demonstrate pancreatic calcification in 30% of cases
- **Abdominal ultrasound or CT** to detect calcifications, dilated ducts and atrophic gland
- **ERCP** is most sensitive test and may show dilated ducts, intraductal stones, strictures or pseudocyst
- **Tests of pancreatic function:** assess endocrine and exocrine function, including glucose tolerance test (see chapter on diabetes mellitus). For exocrine function do ecretin test.
- **Stool tests:** faecal chymotrypsin

Treatment

- Alcohol intake should be avoided.
- At times, IV fluids and fasting prove beneficial.
- Use of oral pancreatic enzymes (30.000 U of lipase) with each meal may improve symptoms.
- If steatorrhea is particularly severe and refractory, medium chain triglycerides, which are absorbed without pancreatic enzymes, can be provided as an alternative source of fat.
- Supplementation with fat-soluble vitamins (A, D, K) is sometimes required.
- Relapse may require treatment similar to that of acute pancreatitis.
- A pancreatic pseudocyst, which causes chronic pain, needs referral to centres with surgical facilities and expertise, where it can be decompressed into a nearby structure to which it firmly adheres (e.g., the stomach) or into a defunctionalized loop of jejunum.

- Diabetes mellitus rarely occurs in chronic pancreatitis. For most patients, serum glucose level of 200 to 250 mg is acceptable and doesn't require treatment. It is better to maintain the patient in a slightly hyperglycaemic range than run a risk hypoglycaemia caused by overzealous administration of insulin.
- Patients with chronic pancreatitis are at increased risk for pancreatic cancer. Worsening of symptoms, especially with development of a pancreatic duct stricture, should prompt an examination for malignancy.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Acute and chronic pancreatitis, 1895-1906.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Diseases of the pancreas, pages 240-244.

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5. Hepatitis

Learning objectives: at the end of this unit the student will be able to

1. *Define acute and chronic hepatitis*
2. *List the etiologies of acute and chronic hepatitis*
3. *Explain the routes of transmission of the different hepatitis viruses*
4. *Describe the clinical features of acute and chronic hepatitis*
5. *List the common complications acute and chronic hepatitis*
6. *Identify the antigens and antibodies used for the diagnosis of viral hepatitis*
7. *Make a diagnosis of acute and chronic hepatitis &*
8. *Refer patients to hospitals for better diagnosis and treatment*

- Hepatitis is a broad category of clinico-pathologic conditions resulting from viral, toxic, pharmacologic or immune mediated damage to the liver.
- Hepatocellular necrosis and inflammatory cell infiltration of the liver are common pathologic features.
- There are two types of hepatitis, which are defined based on duration:
  - ***I. Acute hepatitis:*** lasts for about 6 months or less.
  - ***II. Chronic hepatitis:*** sustained inflammatory response for over 6 months.

5.1 Acute hepatitis

Etiologies:

1) Viruses are the commonest causes, and include hepatitis A, B, C, D, E, G, viruses and other viruses such as EBV, CMV etc.

2) Toxins (amanita phylloides in mushroom poisoning; carbon tetrachloride).

3) Drugs: acetaminophen, INH, halothane, chlorpromazine, erythromycin, heavy alcohol intake

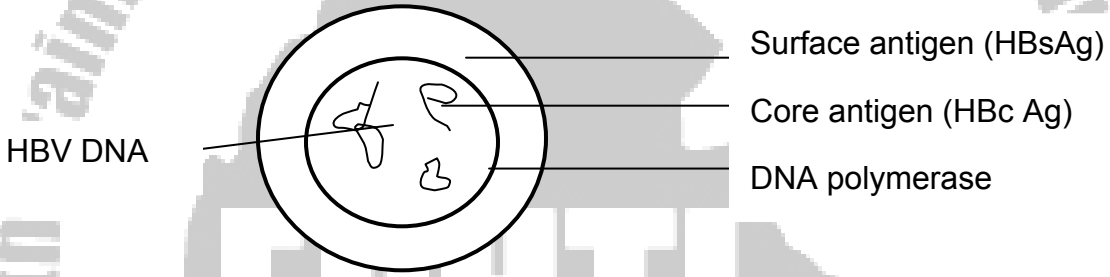
4) Others

a. Wilson's disease

b. Herbs

5.1.1 Acute viral Hepatitis

- Is the most common form of acute hepatitis; Caused by hepatitis viruses (designated as HV) HAV, HBV, HCV, HDV, HEV, HGV (Non A. Non B virus), all of which are RNA viruses except HBV, which is a DNA virus.
- HDV is an incomplete RNA virus and requires the presence of HBV to cause infection. Thus, it causes hepatitis when HDV infection occurs at the same time as HBV infection (HDV co-infection) or in patients with chronic hepatitis B infection (super infection).
- The complete HBV (Dane particle) consists of several antigenetically distinct components, including a surface coat (hepatitis B surface antigen [HBsAg]) and a core of circular DNA, DNA polymerase, hepatitis B core antigen (HBc Ag), and hepatitis B envelope antigen (HBe Ag).



Transmission

- In HAV and HEV transmission is feacooral. Both viruses are implicated in most instances of water borne and food transmitted infection, and in epidemics of viral hepatitis.
- HBV is mainly transmitted by parenteral (via blood and blood products, contaminated needles), sexual contacts and perinatal route. The virus is found in all body fluids and excreta.
- Like HBV, HCV is largely transmitted parenterally. It is the main cause of post transfusion hepatitis, especially before the discovery of anti HCV antibodies. The virus is transmitted less frequently through the sexual and perinatal routes.

Clinical and laboratory manifestations

- **The prodromal phase** lasts for several days and characterized by malaise, fatigue, anorexia, nausea, vomiting, myalgia and headache. Patients will have aversion to smell of food and cigarette with mild fever and flue like symptoms.

- Arthritis and urticaria may be present particularly in HBV which are attributed to immune complex deposition.
- **Jaundice appears late**, usually when the patients start to improve in their sense of well being. It may be absent (Nonicteric hepatitis) in some patients.
- Dark urine and pale stool is common in cholestasis
- The liver is usually tender and enlarged, and splenomegaly occurs in 20% of the cases.

Laboratory

1) ***Liver enzymes:*** Damage to hepatocytes causes release of intracellular enzymes like alanine transaminase (ALT), and aspartate transaminase (AST). Normal levels range between 0 and 35 U/L. In acute hepatitis, they often rise to 20 fold or more.
2) ***Serum bilirubin:*** normal levels range between 0.3 and 1 mg/dl. when levels go above 2.5 -3.0 mg/dl jaundice appears (called icteric hepatitis)
3) ***Alkaline phosphatase*** may be increased by about 3 fold except in cholestatic hepatitis, in which the increment is very much higher.
4) ***CBC:*** leucopenia with atypical lymphocytes (relative lymphocytosis) is common.
5) ***Serodiagnosis:*** serodiagnosis involves antigen/antibody detection.
   - It allows the identification of etiologic agents
   - It helps in planning of preventive and other public health measures for close contacts of infected people
   - It helps in evaluating the prognosis.

   a) ***Diagnosis of HAV*** can be made by detection of anti HAV antibody, which is IgM initially and IgG later on. The IgG antibody confers lifelong immunity.

   b) ***Diagnosis of HBV infection*** The following antigens and antibodies can be detected to HBV infection and help in diagnosis , monitor disease progress , infectivity, and predict the prognosis:

      i) Antigens

      (1) **HBsAg** :

      - Usually cleared within 3 months. It may persist in some patients for 6 months to one year without complications.
      - Its clearance from the blood precedes the appearance of anti-HBs antibody with a time gap in between (known as the window period), during which the only evidence of HBV infection may be anti-HBc antibody.

(2) **HBeAg** indicates HBV replication and high chance of infectivity to others

ii) Antibodies

(1) **Anti HBs antibody** – confers long term immunity

(2) **Anti HBc** - IgM indicates recent infection , IgG indicates remote infection

(3) **Anti HBe :** active infection

N.B. Anti-HBc and Anti-HBe do not provide immunity.

c) **HDV** can be diagnosed by detection of anti HDV antibody.

d) **HCV** is diagnosed by detecting anti HCV antibody.

Table V -5-1. Comparisons of some features of hepatitis A, B, and C

Feature	***Hepatitis A***	***Hepatitis B***	***Hepatitis C***
Incubation	15 to 45 days (mean 30)	30 to 180 days (mean 60 to 90)	15 to 160 days (mean 50)
Onset	Acute	Often insidious	Insidious
Age preference	Children, young adults	Any age	Any age but more common in adults
Transmission Route			
Fecal-oral	+ + +	-	Unknown
Other non-percutaneous routes	±	+ +	+ +
Percutaneous	±	+ + +	+ + +
Other Characteristics			
Severity	***Mild***	***Often severe***	***Variable***
Prognosis	Generally good	Worse with age, debility	Moderate

Progression to chronicity	None	Occasional (5% to 10%)	Frequent (65% -85%)
Prophylaxis	Immunoglobulin /hepatitis A vaccine	Standard IG (not documented), HBIG, HB vaccine	None
Carrier	None	0.1% to 30%	Exists but prevalence unknown

Complications

1) ***Cholestatic hepatitis –***
   - Occurs most commonly during HAV and HEV infection
   - Self limited
   - Pruritus is a common symptom
   - Marked conjugated hyperbilirubinemia presenting with dark urine and pale stool
   - Increased alkaline phosphatase

2) ***Fulminant hepatitis*** **:** in about 1% of cases
   - Is defined as the onset of encephalopathy occurring within 8wks in a patient with acute liver disease
   - Associated with massive hepatocellular necrosis
   - Commonly follows HAV, HBV (usually super infection of HBV infection by HDV), HCV and HEV (in pregnancy)

3) ***Chronic hepatitis***
   - Occurs in HBV and HCV infection
   - Manifest with persistently increased AST and ALT for over 6 months,
   - **Slowly resolving HBV infection** may persist for 6-12 m with eventual complete resolution
   - **Persistent HBV infection** (persistence of HBsAg) without evidence of liver damage resulting in asymptomatic or “healthy” HBV carriers.

Management

- Mainly supportive
  - Rest to limit fatigue
  - Maintain hydration
  - Adequate dietary intake
- Vitamin supplementation has no proven value but vitamin K can be given if there is prolonged cholestasis.
- Alcohol should be avoided until serum transaminases normalize
- Metochlopromide (plasil) – for nausea
- ***Admission***
  - Patients with severe nausea and vomiting.
  - Patients with deteriorating liver function, especially those with encephalopathy or prolonged prothrombin time.
- In general HAV may be regarded as non-infectious after 2 - 3 wks. HBV is potentially infectious to contacts throughout its course, although the risk is low once HBS antigen has cleared.
- Interferon treatment is effective for HCV infection

Prevention

Prevention of HAV and HEV

- General hygienic measures – Hand washing after toilet use; careful handing, disposal and sterilization of excreta and contaminated clothing and utensils.
- For close contacts of HAV infected people
  - Immune serum globulin (IgG) as soon as possible but no later than 6 wks after exposure
  - Active immunization

Prevention of HBV infection

- Meticulous disposal of contaminated needles and other blood contaminated utensils
- For close contacts of HBV infected patients, give HBIG within 7 days and subsequently HBV vaccine (~ HBsAg)
- Dose of HBV vaccine
  - 2.5μg for < 11 yr (when mother is HBsAg - Ve)
  - 5 μg for 11 – 19 yr & children < 11 yr born to HBsAg positive mother

- 10μg for immunocompetent adult.

5.1.2 Alcoholic Fatty liver and Hepatitis

Alcohol abuse is the most common cause of liver disease in the western world. Three major pathologic lesions resulting from alcohol abuse and appearing as stages/spectrum of the disease:

1. Fatty liver
2. Alcoholic hepatitis
3. Cirrhosis

The first two are potentially reversible, but the last one is not.

1. **Alcoholic fatty liver**: is characterized by
   - Right upper quadrant pain
   - Incidentally discovered tender hepatomegally
   - Jaundice is rare, transaminases are mildly elevated (< 5X normal).
   - Completely reversible on cessation of alcohol
2. **Alcoholic Hepatitis**: is severe and prognostically ominous lesion and characterized by the following pathologic triads:
   - Mallory bodies (intracellular eosinophilic aggregates of cytokeratins), usually seen near or around nuclei
   - Infiltration by polymorphnuclear leukocytes
   - A network of interlobular connective tissues surrounding hepatocytes and central veins (spider fibrosis)

Clinical manifestations of alcoholic hepatitis: include

- Weight loss, anorexia, nausea, vomiting and abdominal pain are common presenting symptoms.
- Hepatomegally is found in 80% and splenomegaly is often present
- Fever
- Jaundice, spider angioma, palmar erythema, gyneacomastia and loss of body hair.
- Ascites and encephalopathy may be present and indicate severe disease.
- CBC strikingly elevated. Transaminases modestly increased (200 – 400 IU/l).

- The ratio of ASAT to ALAT frequently exceeds one in contrast to viral hepatitis in which the ratio is approximately one.
- Prolonged prothrombin time, hypoalbuminemia and hyperglobulinemia may be found.

Complications and prognosis

- Alcoholic Hepatitis can reverse with cessation of alcohol, but more commonly progresses to cirrhosis.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Acute hepatitis, pages 1822-1842.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Diseases of the liver, pages 249-264.

EPHTI Ethiopia Public Health Training Initiative

6. Chronic Liver Diseases

Learning objectives: at the end of this unit the student will be able to

1. *Define chronic liver diseases*
2. *List the etiologies of chronic liver diseases*
3. *Describe the clinical features of chronic liver diseases*
4. *List the common complications of chronic liver diseases*
5. *Make a presumptive diagnosis of chronic liver diseases*
6. *Refer patients to hospitals for better diagnosis and treatment*

Chronic liver diseases include:

A. Chronic hepatitis
B. Liver cirrhosis
C. Hepatocellular carcinoma (Hepatoma)

A. Chronic hepatitis

Definition: *Chronic hepatitis is d*efined as a hepatic inflammatory process that fails to resolve after 6 months.

Etiologies:

1) Except HAV and HEV, all hepatitis viruses can cause chronic hepatitis
2) Other causes
   a) Drugs like methyldopa
   b) Autoimmune disorders
   c) Idiopathic causes

Pathological classification

1. **Chronic persistent hepatitis** - inflammatory activity is confined to portal areas.
2. **Chronic lobular hepatitis**
   - Inflammatory activity and necrosis are scattered throughout the lobule.
   - Limiting plates of periportal hepatocytes are intact and no periportal fibrosis.
3. **Chronic active hepatitis**:
   - Inflammatory activity in portal areas spills out into the lobule (periportal hepatitis, piecemeal necrosis) in association with necrosis and fibrosis.
   - Thought to have a significant risk for progression to cirrhosis and hepatic failure.

Chronic viral hepatitis

- Complicates about 1% of acute hepatitis B (young, immunocompetent) and 85-90% of acute hepatitis C will develop chronic hepatitis. About 20% of the later will develop cirrhosis in 10-20yrs.
- Subjects with either HBV or HCV infection have greater risk of developing hepatocellular carcinoma

Treatment can suppress hepatic inflammatory activity in 30-40%

- Hepatitis B - therapy is indicated for patients positive for HBsAg and HBcAg (High replicative phase). Treat with interferon α and Lamivudine.
- Hepatitis C can be treated with interferon α and ribavirin

B. Cirrhosis of the liver and its complications

- It is the end result of fibrous scarring and hepatocellular regeneration, that constitute the major responses of the liver, to a variety of long standing inflammatory, toxic, metabolic and congestive insults.
- The normal hepatic lobular architecture is replaced by interconnecting bands of fibrous tissue surrounding nodules derived from foci of regenerating hepatocytes.
- The following pathologic changes are the cause of the clinical manifestations and complications of cirrhosis

1) Fibrous scarring and disruption of hepatic architecture distort vascular bed leading to Portal hypertension and intrahepatic shunting
2) Disturbed hepatocellular function

Clinical and laboratory features resulting from Hepatocellular dysfunction

- Hypoalbuminemia
- Decreased coagulation factors resulting in prolonged prothrombin time
- Hyperbilirubinemia
- Increased blood ammonia level
- Hepatic encephalopathy
- Ascites

Portal HTN

- Ascites.

- Varices
- Splenomegaly causing thrombocytopenia and leucopenia.
- Hepatic encephalopathy

Major causes of Cirrhosis

1) Alcohol and HCV are major causes in western world
2) HBV is the commonest cause in developing countries
3) Other causes include:
    - o Biliary obstruction (Intrahepatic and extrahepatic) leading to Biliary cirrhosis
    - o Autoimmune hepatitis.

Major complications of cirrhosis

1) Portal Hypertension (HPN)

- Normal portal pressure gradient 10 -15cm of saline
- Portal hypertension is said to exist when the portal pressure gradient is over 30 cm of saline
- Portal hypertension leads to the formation of venous collateral vessels between the portal and systemic circulation. Collateral vessels may form at several sites, the most important clinically being those connecting the portal vein to the azygous vein that form dilated, tortuous veins (varices) in the submucosa of the gastric fundus and esophagus.

Types of portal hypertension

i. ***Presinusoidal portal HPN*** – increased resistance to portal blood flow into the liver
E.g. Schistosomiasis causes periportal fibrosis and presinusoidal portal HPN

ii. ***Sinusoidal portal HPN*** – is the commonest and found in cirrhosis. The resistance is in the sinusoids of the liver.

iii. ***Post sinusoidal portal HPN*** – increased resistance to hepatic venous outflow from the liver and causes include hepatic vein thrombosis and congestive heart failure.

2) Variceal hemorrhage

- Esophageal varices – has a mortality of 30-60% if it bleeds
- May present with hematemesis, melena, hematochezia

Treatment of Variceal hemorrhage depends on the speed and volume of bleeding.

- Acutely bleeding patients should be referred to hospitals for intensive care.
- Resuscitation

Medical Therapy

- Somatostatin (or octreotide) reduces splanchnic blood pressure when given intravenously
- Vasopressin with nitroglycerin help to minimize systemic vasoconstriction
- Endoscopic therapy includes injection of sclerosing agent and/or band ligation of varices.
- Balloon tamponade – compressing bleeding varices temporarily

Surgery: portosystemic shunt

Prevention of variceal hemorrhage:- the following drugs can be given for patients diagnosed to have CLD. They are not given during active variceal bleeding.

- Non selective β-blockers (propranolol and nadolol)
- Mononitrates (Isosorbide mononitrate) decrease portal blood flow and pressure

3) Ascites

- Transudative
- Serum to ascitic albumin gradient is > 1.1
- Clinically detectable when larger than 500 ml
- Most sensitive clinical sign is shifting dullness
- Subclinical ascites can be detected by ultrasound examination.

Management of ascites

- Salt restriction to less than 2g/day
- Fluid restriction if serum Na^+ level is below 120 meq/l
- Spirinolactone (aldactone) is an aldostrone antagonist, is often effective when given with loop diuretics.
- Duiresis should be monitored because vigorous duiresis leads to hypovolemia and hypokalemia and precipitate hepatic encephalopathy. The goal of duiresis should be dependent on the extent of edema and be monitored by daily body weight measurement i.e.
    - Decrease weight by 0.5 kg/day if no peripheral edema and
    - Decrease weight by 1kg/day if peripheral edema is present.

Refractory ascites:

- Is defined as persistent tense ascites despite maximal diuretic therapy (Spirinolactone 400 mg/d, Furesemide 160 mg/d), or if azotemia develops (creatinine > 2mg/dl) while the patient is receiving sub maximal doses.

- It occurs in 10% of ascites of CLD origin. Such patients should be referred to hospitals for treatment:
  - Repeated large volume paracentesis (with intravenous albumin replacement if available). But the following two modalities of therapy are available in developed countries.
  - Surgical treatment (Porto-systemic shunt)
  - Liver transplantation

Complications of ascites

- Spontaneous bacterial peritonitis
- Hepatopulmonary syndrome
- Hepatorenal syndrome
- Rupture of the umbilicus

a) Spontaneous bacterial peritonitis(SBP)

- Usually due to *enterobacteriacae* or *pneumococci*
- Characterized by fever, abdominal pain and tenderness. Hepatic encephalopathy may be precipitated by the infection.
- Diagnosis is suspected when ascitic polymorphonuclear cell count is over 250/μl. and confirmed by ascitic fluid culture.
- Treatment is with third generation cephalosporin for 5 -7 days.

Prophylaxis for SBP

Indications

- Previous history of SBP
- Patient admitted with gastrointestinal hemorrhages.
- Ascitic protein less than 1gm/dl
- Candidates of liver transplantation

Drugs

- Norfloxacin – 400 mg/day
- Ciprofloxacin – 750 mg/once weekly or
- Co-trimoxazole - 960mg/d for 5 days (Monday – Friday)

b) Hepatorenal syndrome(HRS)

- Functional renal failure in the presence of cirrhosis.

- Occurs when there is significant hepatic synthetic dysfunction and severe ascites.
- Vigorous duiresis , paracentesis and sepsis may predispose to HRS
- Typically the kidneys are histologically normal with the capacity of regaining normal function in the event of recovery of liver function. There is severe cortical vasoconstriction
- Characterized by declining GFR, oliguria, low urine sodium (< 10 mg/l), normal urinary sediment and azotemia often with disproportionately high levels of blood urea nitrogen and creatinine
- Diagnosed after prerenal cause of renal failure is excluded.
- Mortality rate from HRS is 95%

Management of HRS

- Volume expansion to rule out volume depletion
- Low dose vasopressin, octreotide or norepinephrine may be given
- Liver transplantation is the accepted management.

4) Hepatic encephalopathy (Hepatic coma or portosystemic encephalopathy)

It is a complex neuropsychiatric syndrome that may complicate advanced liver disease and/or extensive portosystemic shunt. It manifests in two major forms: acute and chronic.

Acute

- Occurs in the setting of fulminant hepatitis
- Cerebral edema plays a more important role
- Mortality rate is very high

Chronic

- Occurs in chronic liver disease
- Often reversible

Pathogenesis

- The hepatocellular dysfunction and portosystemic shunt leads to inadequate removal of nitrogenous compounds and toxins ingested or produced in the gastrointestinal tract, getting access to the brain and causing hepatic encephalopathy.
- The compounds commonly incriminated in causing hepatic encephalopathy include
    - Ammonia is very well known and studied
    - GABA

- Mercaptans – a cause of fetor hepaticus in CLD
- Short chain fatty acids

Clinical Features may involve

- Disturbance of higher neurologic function
- Intellectual and personality disorder
- Dementia, inability to copy simple diagrams (constructional apraxia)
- Disturbance of consciousness
- Disturbance of neuromuscular function (asterixis, hyperreflexia, myoclonous)
- The findings are usually asymmetrical, but can also be symmetrical
- The manifestations depend on the stage of hepatic encephalopathy

Table V-6-1. Stages of chronic hepatic encephalopathy and their manifestations

Stage	***Clinical manifestation***
I	Apathy, restlessness, reversal of sleep rhythm, slowed intellect, impaired computing ability, impaired hand writing
II	Lethargy, disorientation, drowsiness, asterixis
III	Stupor (arousable), hyper active reflexes, extensor plantar responses
IV	Coma

Treatment of chronic hepatic failure is based on four principles

1) Identify and treat precipitating factors including

- GI bleeding
- Increased dietary protein
- Constipation
- Alkalosis
- Hypovolemia
- Infection
- Azotemia
- Hypokalimia from overduiresis

- CNS depressant drugs

2) ***Reduce and eliminate substrates for the generation of nitrogenous compounds.***
   - *Restrict dietary protein*
     - For patients in coma no protein should be given
     - For non comatose patients restriction of protein to 40 - 60 gm/d is enough.
   - *Cleanse the bowel with enema in patient with gastrointestinal hemorrhage*
3) ***Reduce colonic bacteria*** that generate ammonia using oral preparations of Neomycin or Metronidazole
4) ***Prevent diffusion of ammonia from the bowel lumen to the blood by administering oral*** lactulose, lactitol, or lactose (in lactase deficient patients) all of which are fermented by colonic bacteria to organic acids and reduce stool PH. The hydrogen ion produced traps ammonia in the colon and changes it to nondiffusable NH_4^+ ions.

Hepatopulmonary syndrome

- Characterized by abnormal arterial oxygenation in a patient with cirrhosis and/or portal HTN.
- Pathogenesis is thought to be due to intrapulmonary vasodilatation leading to impaired O_2 transfer that improves with 100% O_2
- Clinical features range from sub clinical abnormalities in gas exchange to profound hypoxemia causing dyspnea at rest.
- It is a functional disorder that reverses with liver transplantation.

C. Hepato cellular carcinoma (Hepatoma)

- One of the most frequent malignancies and important cause of mortality particularly in middle aged men in developing countries. The incidence is less in developed countries
- Arises in cirrhotic liver and is closely associated with chronic hepatitis B or C.
- Hepatitis B DNA has been shown to integrate in to the host cell genome, where it may disrupt the tumor suppressor genes and/or activate oncogenes.
- Vaccination prevents hepatitis B infection, thereby reducing the incidence of hepatoma
- More common in males (male to female ratio 4:1 to 8:1)

Clinical and Laboratory findings

Common symptoms and findings

- Abdominal pain
- Weight loss
- Abdominal mass
- Derangement of liver function

Unusual manifestations

- Bloody ascites
- Tumor emboli
- Jaundice
- Gyneacomastia
- Hepatic bruit or friction rub
- Metabolic effect
  - Erythrocytosis
  - Hypercholesterolemia
  - Hypoglycemia
  - Hypercalcemia
  - Acquired porphyria
- High serum α fetoprotein level (> 400 mg/dl)
- Ultrasonography :Mass lesion with varying echogenicities but usually hypoechoic
- Tissue specimen: may be required to confirm the diagnosis
- Median survival rate is less than 6 months from the time of diagnosis

Treatment: is usually unsatisfactory but some options include:

- Chemotherapy
- Radiotherapy
- Liver transplantation.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Chronic Hepatitis , Cirrhosis and it complications, pages 1844-1868.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Diseases of the liver, pages 249-264.

7. Diarrheal diseases

Learning objectives: at the end of this unit the student will be able to

1. *Define diarrhea*
2. *List the etiologies of acute and chronic diarrhea*
3. *Explain the mode of transmission of organisms causing diarrhea*
4. *Describe the clinical features of diarrhea*
5. *List the common complications acute and chronic diarrhea*
6. *Make a diagnosis of acute and chronic diarrhea*
7. *Manage patients with diarrhea at the primary care level*

***Definition*:** Diarrhea is defined as an increase in stool frequency and volume. The stool is usually liquid, and 24 hrs output exceeds 250 gm/day

Objective definition – Stool weight greater than 200gm/day.

- Normal stool weight is about 100 - 200 gm/d for people in developed countries who usually consume diets containing less fiber.
- Stool weight is affected by fiber contents of diet, gender (higher in males), medications, possibly exercise and stress.
- Normal bowel habit ranges from 3 times/day to 3 times/wk. Thus, one has to know the normal bowel habit of the individual and the nature of the current symptoms before the diagnosis of diarrhea
- About 9 liters of fluid is presented to the GIT daily (7 liters from the secretion and 2 liters from diet). Of this only 100 - 200 ml of fluid is excreted with feces and the rest will be reabsorbed. Fluid absorption follows Na^+ absorption, which is co-transported with chloride ion, glucose, and aminoacids and through Na^+ channels.
- Na – glucose co-transport is unaffected by many diarrheal diseases
- Secretion follows chloride ion secretion in crypt cells, with Na^+, K^+ and water following passively through tight junctions.

Classification of diarrhea

1. ***Based on the duration of illness diarrhea can be classified into acute and chronic***

A) ***Acute diarrheal disease***

- Lasts for 2 - 4 wks

- It is usually infectious in origin
- Resolves with or without intervention

B) Chronic diarrheal diseases

- Lasts for more than 4 wks
- The common causes include malabsorption, inflammatory Bowel Diseases (ulcerative colitis), irritable Bowel syndrome, colonic cancer, and HIV/AIDS.
- Infectious causes are not common causes of chronic diarrhea

2. Based on the nature of diarrheal stool, acute diarrhea could be inflammatory or non-inflammatory

A) Non-inflammatory diarrhea

- Is watery, non bloody diarrhea associated with periumblical cramps, nausea, and vomiting
- It is small intestinal in origin

B) Inflammatory diarrhea -

Dysentery is bloody diarrhea

3. Pathophysiologic classification

Most diarrheal states are caused either by inadequate absorption of ions, solutes and water or by increased secretion of electrolytes that result in accumulation of water in the lumen.

Based on this concept diarrhea can be classified as:

A) Secretory diarrhea:

- Occurs when the secretion of fluid and electrolytes is increased or when the normal absorptive capacity of the bowel is decreased. It usually follows stimulation by mediators like enteric hormones, bacterial enterotoxins (E.g. *Cholera,* heat labile *E. coli* toxin, *Salmonella enterotoxin*), vasoactive intestinal peptides (VIP) or laxatives . These agents activate the adenyl cyclase –cAMP system
- These mediators block Nacl absorption and induce chloride secretion. These events can result in massive diarrhea, without evidence of cell injury, as shown by the ability of the cell to absorb Na^+ if coupled to nutrients (Na^+ to glucose, Na^+ to amino acids). That is why cholera and other forms of secretary diarrhea can be treated with oral solutions containing sodium and glucose.
- Diarrhea of secretary origin persists even if the patient fasts.

B) Osmotic diarrhea:

- It occurs due to the presence of poorly absorbed or nonabsorbable substance in the intestine which is osmotically active , resulting secondary accumulation of fluid and electrolytes. Such nonabsorbable substances include lactose in patients with lactase deficiency.
- This type of diarrhea is usually caused by malabsorption and disappears when patient fasts for 48-72 hrs.

C) ***Abnormal intestinal motility****:* causes or contributes to diarrhea seen in Diabetes mellitus , irritable bowel syndrome , postvagotomy states , carcinoid syndrome and hyperthyroidism, Mechanism of abnormal intestinal motility includes the following

- If small bowel peristalsis is too rapid , an abnormal large amount of fluid and partially digested foodstuffs may be delivered to the colon
- Extremely slow peristalsis may allow bacterial overgrowth to occur, and bile salts deconjugation to cause secondary malabsorption
- Rapid colonic motility may not allow adequate time for the colon to absorb fluid delivered to the cecum (Normally 90 % of the fluid is absorbed)

D) ***Exudation*****:** inflammations or infectious conditions that result in damage to the intestinal mucosa can cause diarrhea by a number of mechanisms. There is loss of blood, mucous proteins and serum proteins. Mucosal damage can interfere with absorption, induce secretion and affect motility, all of which contribute to diarrhea.

Infectious Diarrhea

Microbes cause diarrhea either directly by invasion of gut mucosa or indirectly through elaboration of different types of toxins: Secretory enterotoxins, cytotoxins and inflammatory mediators.

I) Secretory toxin induced diarrhea

- Patients seldom have fever or major systemic symptoms.
- Little or no inflammatory response.
- The organisms colonize the intestinal mucosa but don't invade the intestinal wall.

Examples:

a) *Vibrio cholerae* produces enterotoxins which stimulate adenylate cyclase which results in massive intestinal secretion.

b) *Enterotoxigenic E. coli* is the major cause of traveler's diarrhea

c) Non typhoidal salmonella like *S. typhimarium*

d) *Shigella dysenterae* may initially cause secretary diarrhea.

II) Cytotoxin induced Diarrhea Cytotoxins are soluble factors that directly destroy mucosal epithelial cells. Examples:

a) Shigella dysenterae produces Shiga toxin which causes destructive colitis.

b) Enterohemorrhagic E.coli

c) Clostridium perifringens, Vibrio parahemolyticus

d) Clostridium defficile causes psudomembraneous colitis in individuals treated with antibiotics.

III) Diarrhea caused by invasive pathogens.

- Characterized by fever and other systemic symptoms like headache and myalgia.
- The diarrhea is frequent but small in volume. It is associated with crampy abdominal pain and tenesmus.
- These pathogens induce marked inflammatory response and stool usually contains pus cells, proteins and often gross blood.

Common causes include :

Acute shigellosis

- Feaco-orally transmitted, as few as 10 - 100 bacteria are enough to cause diarrhea
- Initially multiplies in the small intestine causing secretary diarrhea. Later it invades colonic epithelium causing bloody diarrhea.
- Usually resolves spontaneously after 3 - 6 days.

Acute Salmonellosis

- Transmitted by ingestion of contaminated meat, dairy or poultry products.
- The non typhoidal salmonellae invade primarily the distal ileum.
- Causes short lived (2 – 3 days) illness characterized by fever, nausea, vomiting and diarrhea. This is in marked contrast to the 3 - 4 wks febrile illness caused by Salmonella typhi and paratyphi, which are not usually associated with diarrhea.

Campylobacter jejuni

- It may be responsible for up to 10% of acute diarrhea world wide. It invades both the small and large intestines.

Enterohemorrhagic E. coli ;

- It produces bloody diarrhea without evidence of mucosal inflammation (grossly bloody stool with few or no leucocytes).

Viral causes of diarrhea **e.g.** Norwalk and Rota viruses

- Invade and damage villous epithelial cells
- Cause diarrhea by interfering with absorption through selective destruction of absorptive villous tip cells with sparing of secretary crypt cells.
- Stool is usually watery and its content resembles those of noninvasive diarrhea, with few inflammatory cells, probably because of absence of colonic damage.

Protozoal cause of diarrhea

a) Giardia lamblia.

- few organisms are necessary to cause infection
- Multiplies in the small intestine, attach to and occasionally invade the mucosal cells.
- Its clinical features span from an acute diarrheal illness to chronic diarrhea associated with malabsorption and weight loss
- Diagnosis is based on identification of the organism either in the stool or duodenal mucus or by small intestine biopsy. Cysts or trophozoites can be identified in the stool, and treatment should be given in both cases.

b) Entamoeba histolytica may cause syndromes ranging from mild diarrhea to fulminant amoebic colitis with multiple bloody stools, fever and severe abdominal pain.

c) Cryptosporidium parvum and Isospora belli occasionally cause self limited acute diarrheal illness in otherwise healthy individuals. They may cause voluminous life threatening diarrheal diseases in patients with acquired immunodeficiency syndrome. Modified acid fast staining of the stool will identify both organisms.

Evaluation of a patient with diarrhea

Careful interview of patients with diarrhea contributes in etiologic diagnosis, evaluation of severity of illness, and in designing treatment and preventive measures. Thus, the history should include

Duration of illness: if the diarrhea lasts for 2 - 4 wks, acute diarrheal diseases are said to exist. These are usually infectious in origin and resolve with or without intervention. However, if it lasts for more than 4 wks, consider chronic diarrheal diseases and infectious causes are unlikely. In such cases the common causes include malabsorption,

inflammatory Bowel Diseases (ulcerative colitis), irritable Bowel syndrome, colonic cancer, and immuno suppressions like AIDS.

Diurnal variation – is there any relation to any part of the day?

- Nocturnal – organic causes
- Non nocturnal – functional causes like irritable bowel syndrome

Is the diarrhea watery or bloody?

Bloody diarrhea is usually inflammatory or ischemic in origin and caused by invasive organisms, ulcerative colitis, or neoplasms

Volume of diarrhea

Large volume diarrhea indicates small bowel or proximal colonic diseases

Scanty, frequent stools associated with urgency suggest left colon or rectal diseases

Any association with specific meal? If diarrhea is associated with intake of

Fat – it is due to fatty intolerance

Sweet diet – it is due to osmotic diarrhea

Milk and milk products - it is due to lactase deficiency

Is there history of drug intake?

Penicillin may be associated with psudomembraneous colitis.

Laxatives

Chemotherapeutic agents

7) Presence of underlying diseases (like diabetes mellitus) or systemic symptoms

Physical examination: Assess severity of dehydration, Wight loss and other associated signs in patient with chronic diarrhea.

Diagnosis:

Laboratory tests:

1) ***Culture and sensitivity testing to*** detect a pathogenic bacterial strains. A positive stool culture is found for 40 % of patients who have WBC in the stool and fever
2) ***Microscopic examination:*** to identify ova and parasites
3) ***Guaiac :*** to detect occult blood
4) ***Sudan staining:*** to detect fat droplets.
5) ***Wright or methylene blue staining:*** to detect WBC, which are indicative of invasive infectious causes of diarrhea.

Proctosigmoidoscopy: to exclude of confirm the diagnosis of inflammatory bowel diseases.

Management

1. Rehydration

- In patients with massive diarrhea and vomiting with hypotension intravenous fluids like Ringer's lactate or Normal saline should be given in adequate amount.
- For patients without hypotension oral fluid containing sodium, glucose, potassium and chloride ions (ORS) are preferred.

2. Antimicrobial therapy

Antibiotics:

- Most acute infectious diarrheal diseases do not require antibiotic therapy because majority of them are self limited and viral in nature.
- Of the non invasive bacterial diarrhea, antibiotics decrease the volume of diarrhea only in cholera. Doxycycline 300mg single dose is the drug of choice.
- For invasive bacterial diarrhea caused by *E. coli* and *Shigella* (bacillary dysentery) Ciprofloxacin 500 mg or Norfloxacin 400mg twice a day for 3-5 days is indicated.

Anti-protozoal:

- For *Entamoeba histolytica*: Metronidazole 500mg PO TID for 7 days
- For *Giardia lamblia:* Metronidazole 250mg thrice a day for 5 days or Tinidazole 2g once.
- For *Isospora belli:* Co- trimoxazole 960mg four times a day for 10 days then 960mg twice a day for additional three wks . In immunocompromized patients continue maintenance dose of the same drug three times a week.
- When no specific therapy is available or no cause is identified it's appropriate to give empirical therapy E.g.
  - Antibiotics for possible bacterial overgrowth or Metronidazole for Giardia, cholesteramine for bile acid malabsorption or
  - Non specific therapy with constipating agents such as loperamide, diphenoxylate and in more severe cases codeine or long acting somatostatin analogue.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Diarrhea, pages 225-229.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Diarrhea, 210-224.

CHAPTER SIX
HEMATOLOGIC DISORDERS

1. Anemia

Learning objectives: At the end of this topic the student we be able to:-

1. *Define anemia and describe the diagnostic criteria of anemia in adults.*
2. *Understand factors that influence Hematocrite / Hemoglobin values*
3. *Evaluate cases of anemia with appropriate history, physical examination and proper laboratory studies*
4. *Describe classification of Anemia.*
5. *Understand the adaptive mechanisms to chronic anemia.*
6. *Understand the principles of management of anemia.*

Anemia: General approach

a) Definition

- **Functional definition**: A significant reduction in red cell mass and a corresponding decrease in the 0_2 carrying capacity of the blood.
- **Laboratory definition**: A reduction of the Hemoglobin concentration, red cell mass or Hematocrite, to below normal levels.
- In women of the child bearing age, their blood values are 10% lower than men. Therefore, Anemia may be defined as a HCT of less than 10% below the mean values for age, sex and altitude

Table VI-1-1 Criteria of anemia in adults at sea level

Factor	Women	Men
RBC x 10^{12}/ L	< 4.0	< 4.5
Hgb (g/dl)	< 12	< 14
HCT (%)	< 37	< 40

NB: blood values may not accurately reflect alteration in red cell mass. For instance;

- Hgb or Hematocrite could be falsely elevated (↓ plasma volume) e.g. hemorrhage, burns, vigorous diuresis, dehydration all leading to *Hemoconcentration*
- Hgb or Hct may be falsely low (↑ plasma volume) leading to *Hemodilution*
  E.g. Spleenomegaly, CHF, Cirrhosis, pregnancy

Epidemiology

- In Ethiopia, a study conducted by Zein Ahmed Zein in Gondar, rural population indicated a prevalence rate of anemia to be very high (40.5%,), and anemia was the fourth leading cause of hospitalization and hospital deaths in 1982 in Gondar.
- Another study done in Black lion Hospital in 1987 G.C. showed that anemia is the 3rd cause of hematology admissions.
- Analysis of admissions to hospitals in Ethiopia showed that anemia accounted for 0.5 - 4% of all admissions and 25% of hematological diseases related admissions.
- Iron deficiency anemia is the commonest type of anemia globally, mainly in developing countries like Ethiopia.
- Sickle cell disease and thalassemias are not reported in Ethiopia but common in other African countries. Hereditary hemolytic anemias aren't common in our country.

Clinical approach to the Patients with anemia

Anemia is a manifestation of an underlying pathological condition.

It results from:

1. Under production
2. Increased destruction/Hemolysis
3. Blood loss /bleeding
4. Multifactorial : a combination of these

History: Accurate history provides information crucial to the diagnosis of the underlying cause.

- Nutritional /Dietary history
- Underlying diseases
- Blood loss : GI or Genito uirinary blood loss
- Family history of anemia
- Exposure to drugs/toxins E.g. - Methyldopa
- Ggeographical location

- Pregnancy

Symptoms:

- Depend on the rapidity of development of anemia, age of the patients, the presence of an underlying disease .They are often non-specific
- Fatigue, dizziness, dyspnea, palpitation, syncope, exercise and cold intolerance, angina,
- Tinnitus, vertigo, throbbing head ache,
- Anorexia, indigestion, nausea, bowel irregularity (due to shunting of blood from the splanchinic bed)
- Irritability, difficulty in concentration, worsened dementia and.
- Impotence or decreased libido
- Intermittent claudication

Physical Examination:

A comprehensive examination with emphasis to the following findings should be made.

- Skin and mucous membrane: look for pallor, icterus, bleeding sites, leg ulcer
- Spooning of fingernails $\rightarrow$ in iron deficiency anemia
- Atrophy of the tongue, sore tongue (glossitis), angular stomatitis which may be seen in iron deficiency anemia.
- Abdomen: spleenomegaly, hepatomegaly, evidence of gallstone.
- Pelvic and rectal examination: to look for possible site of bleeding.
- Bone tenderness and Lymphadenopathy to rule our hematologic malignancies and
- Neurological: gait, reflexes, vibration and position sense which may help to look for neurologic changes associated with Vit B_{-12} deficnecy.
- Fundoscopy: retinal hemorrhage
- Cardiovascular system; modest tachycardia, wide pulse pressure hyper dynamic precordium, flow murmur. In severe form of Chronic anemia patients may develop CHF with S3 gallops.

Laboratory study

1. ***Complete blood count***

   Hgb, Hct, ESR, Platelet count, WBC with differential

2. ***Red blood cell indices***
    a. Mean Corpuscular volume (MCV): Hct/RBC : normal value is 80 – 95 fl
    b. Mean corpuscular Hemoglobin(MCH) : Hgb/RBC : 27 – 32 pg
    c. Mean corpuscular Hemoglobin (MCHC): Hgb/Hct 32 – 36%
3. ***Examination of the peripheral blood smear:*** examine a cellular morphology, shape, size, color, abnormality of other cells.

Red cell morphology

- Normochromic Normocytic RBCs are aeen in normal individuals and in anemia of chronic diseases
- Anisopoikilocytes: Variation in size and shape may be seen in iron deficiency anemia
- Hypochromic microcytic anemia: is seen in iron defeciency anemia , anemia of chronic diseases , thalassemia and sideroblastic anemia (SBA)
- Macrocytic RBCs : Macro – ovalocytes with hyper segmented neutrophils → indicate megaloblastic anemia and myelodysplasia
- Schistocytes (fragmented RBC/Helmentcells):- microangiopathies , DIC, vasculitis, prosthetic heart valve

Classification of anemia

A. *Pathophyisiologic Classifications* (based on underlying disease)

1) Anemia associated with impaired RBC Production

a) Aplastic anemia
b) Iron deficiency
c) Myelodysplastic syndrome.
d) Megaloblastic anemia
e) Anemia of CRF
f) Anemia of chronic diseases
g) Drug related

2) Anemia associated with increased RBC loss or destruction

a) Bleeding
b) Hereditary hemolytic anemia
    i) Hemoglobinopathies, sickle cell disease, Thalassemia
    ii) Primary disorder of RBCs
    iii) RBC erythropathies (G6 PDH, PK deficiency)
c) Acquired hemolytic anemia

i) Autoimmune
ii) Drug induced hemolytic anemia
iii) Microangiopathies (e.g. DIC)
iv) Traumatic

B. Morphological classification

1) Hypochromic microcytic anemia

a) Inherited: Thalassema, sideroblastic anemia
b) Acquired: IDA, Anemia of chronic diseases

2) Macrocytic anemia : (MCV > 100 fl)

a) With megaloblastic marrow: megaloblastic anemia
b) With normoblastic marrow: Hemolysis, acute bleeding,

3) Normchromic normocytic:-

a) Anemia of chronic disease
b) Early iron deficiency anemia
c) Aplastic anemia
d) Anemia of CRF

Adaptation to chronic anemia*: the main consequence of anemia is tissue hypoxia*

Compensatory mechanisms:

1. Intrinsic red cell adjustments (adaptations)

- Modulation of O_2 affinity by increased generation of 2,3- diphosphoglycerate in erythrocytes
- It bounds to Hgb, causing a right ward shift in O_2- Hgb dissolution curve

  $\Rightarrow$ This allows more O_2 to be unloaded from the RBC at any given blood O_2 tension

2. Cardiovascular adjustment

- **Increased in cardiac output** occurs at Hgb level of 7-8 gm% : the increased in cardiac output coupled with modest **tachycardia** creates a hyperdynamic state and hence systolic ejection murmur
- **Peripheral vascular resistance decreases** there by facilitating tissue perfusion; clinically is evidenced by wide pulse pressure.

3. Local changes in tissue perfusion: Redistribution of blood flow to vital organs at the expense of reduced blood flow to less vital organs.

4. Reduction of mixed venous O_2 tension to increases the arterio–venous O_2 difference $\Rightarrow \uparrow$ O_2 extraction at peripheral tissues

Individuals tend to survive at extremely low hemoglobin levels (even as low as 3 gm %) due to these compensatory mechanisms.

Therapeutic considerations and indications

In the management of anemic patients carefully remember the following points

- Identify and correct the cause of anemia
- Administration of Hematinines such as Iron, Vit B_{12} or folate without correct diagnosis of the cause of anemia is an unacceptable practice in the treatment of anemia
- Therapeutic modalities include: Iron, folate, Vit. B_{12}, pyridoxine (B_6) blood transfusion, steroids (in hemolytic anemia) splenectomy, erythropoietin, bone marrow transplant (aplastic anemia), and androgens
- Carefully weigh the risks of blood transfusion over its advantage.

When to transfuse blood in chronic anemia

1. Anemia severe enough to cause CHF (congestive heart failure)
2. Hypoxic manifestations: Irritability, unconsciousness, angina
3. Surgical or gynecologic patient awaiting surgery

NB: no threshold of Hct/Hgb that mandates transfusion; the decision to administer blood must be based on the functional status and symptomatology of the patient.

- Consider risk of blood transfusion
- Adhere to blood component transfusion (packed RBC, FFP, cryoprecipitate, platelets)
- Consider whole blood only when there is volume loss due to hemorrhage.

I. Micorocytic Anemias

A) Iron deficiency anemia (IDA)

Learning objectives: at the end of this topic the student will be able to:-

1. *Understand iron metabolism*
2. *Describe the characteristic features of iron deficiency anemia (IDA)*
3. *List the various causes of iron deficiency anemia (IDA)*
4. *Know the clinical manifestations and common specific laboratory findings of iron deficiency anemia (IDA)*
5. *List some of the differential diagnosis of iron deficiency anemia (IDA)*
6. *Understand the management of iron deficiency anemia (IDA)*

7. *Identify possible reasons for inadequate response to therapy and indications for parenteral iron administration*
8. *List the possible causes of anemia of chronic diseases with their features, pathogenesis and principles of therapy*

Definition*:* - Iron deficiency anemia occurs when body iron stores become inadequate for the needs of normal RBC production (erythropoiesis)

It's characterized by:

- Hypochromia and microcytosis of the circulating erythrocytes (RBCs)
- Low plasma iron and ferretine concentration.
- A transferrin saturation of < 15% (Normally ~ 35%)

- Iron deficiency anemia is a manifestation of diseases, not by itself a complete diagnosis
- It is the commonest cause of anemia world wide

Introduction

Iron metabolism:

- Daily 10-30mg iron ingested, 5-10% absorbed to balance precisely the amount lost (1mg) under physiologic condition
- Amount absorbed can increases up to *five fold* if body iron store are depleted or erythropoiesis is accelerated.
- Absorbed as hem and non hem iron in the duodenum and proximal jejunum

Iron absorption:

- **Is facilitated by:** Stomach acidity, Ascorbic acid, citrates, while
- **Is limited/reduced by :** Phosphates, Oxalates, TTC, Tannates (tea) and pyrates (plant food)

Transferrin is the transport protein that carries iron in the plasma and ECF.

Sequences of events in the development of IDA

1. *Mobilization and depletion of iron stores*
2. *Decreased plasma Fe^{2+} and Ferretine concentration*
3. *Iron deficient erythropoiesis*
4. *Iron deficiency anemia – Hypo chromic microcytic cells*

Etiologies of Iron deficnecy Anemia

1. ***Chronic blood loss***
   - Uterine

- Gastrointestinal, e.g. esophageal varices; Hiatal hernia; peptic ulcer disease; aspirin ingestion; Carcinoma of the stomach, ceacum, colon or rectum; ***hook worm infestation***; colitis; piles; Diverticulosis; etc
- Rarely hematuria, hemoglobulinuria, pulmonary hemosiderosis, self inflicted blood loss
- Disorders of hemeostasis, intravascular hemolysis

2. Increased demands

- Prematurity in newborns
- Rapid growth (as in adolescent) growth spurt
- Pregnancy

3. Mal absorption of iron

- Gastrectomy, Celiac disease

4. Poor diet

$\Rightarrow$ Contributory factor in many countries but rarely sole cause

Clinical manifestation:

- Is insidious in onset and progressive in course
- Patients often present with nonspecific symptoms mentioned above with/without some specific symptoms.

Specific symptoms

- Pica: craving for unusual food substance (amylophagia, geophagia, pagophagia)
- Increased GI absorption of lead – lead poisoning
- Koilonychia – spooning of the finger nails
- Plummer – Vinson/Peterson - Kelly syndrome: characterized by IDA, koilonychia, and dysphagia due to post cricoid esophageal web)

Laboratory findings

A) Peripheral blood morphology and RBC indices

- ↓MCV, ↓MCH, ↓MCHC and hypochromic microcytic RBCs with occasional target cells and pencil-shaped poikilocytes
- ↓ reticulocyte count
- Dimorphic peripheral films (mixed Normal RBCs and microcytic hypochromic RBCs)
    - Combined Iron and folate /B_{12} deficiency
    - On those with recent iron therapy

- Those with recent blood transfusion

B) Serum iron and total iron – binding capacity (TIBC)

- ↓ serum iron and ↑ TIBC (hence IBC is < 10% saturated). This is in contrast to other forms (e.g. ACD).

C) Serum ferritine is decreased

D) Free erythrocyte protoporphyrine (FEP): non specific

- It increased during early phase of iron deficiency anemia, lead poisoning, sideroblastic anemia and in erythropoietic porphyria.

E) Bone marrow iron

- Complete absence of iron from stores (macrophages) and absence of siderotic iron granules from developing erythroblasts

F) Investigation to establish the underlying cause

- Stool for occult blood
- CXR to exclude pulmonary hemosiderosis
- U/A for hematuria or hemosiderinuria
- Pelvic – gynecologic studies
- Cr^{-} labeling of RBCs with 5 day collection of stools
- Upper and lower GI radiologic and Endoscopic studies
- Bronchoscopy

Differential diagnosis of hypochromic, microcytic anemia

A. With ↓ body iron stores – IDA

B. With normal body or ↑ body iron store

i) Impaired iron metabolism: Anemia of chronic diseases (ACD)
ii) Disorder of globin synthesis: Thalassemia
iii) Disorders of hem synthesis: sideroblastic anemia
iv) Both impaired iron metabolism and defective globin synthesis: lead poisoning

Treatment of Iron deficiency Anemia

1. Identify underlying cause and treat it
2. **Correct anemia** and **replenish stores** by oral iron,
    - ***Ferous sulfate 300mg (60 mg elemental iron)*** 3x/day for 4-6 months

Absorption increased by giving between meals, but side effects are less if given with meals

Common Side effects; GI upset, nausea, dyspepsia, constipation /diarrhea. If the side effects are not tolerable, reduced dose or change brand e.g. to ferrous gluconate or ferrous lactate syrup.

- ***Response to treatment;*** an expected daily rise of hemoglobin by 0.1-0.2 gm /dl in
- **Follow-up**; reticulocytosis will start at 3-4 days and peak on the 10th day of initiation of treatment.
- An increase in Hgb concentration of at least 2gm/dl after 3wks of therapy is considered as a good response.
- Treatment should be continued for about 3 months after resolution of anemia to replenish the iron store.

Inadequate response may imply

- Continuing hemorrhage
- non compliance to therapy
- Wrong diagnosis
- Mixed deficiency – associated folate or vit.B_{12} deficiency
- Another cause for anemia e.g. malignancy, inflammation
- Malabsorption – rare cause
- Use of slow release preparations

Parentral iron

Indications:

1. Oral Iron intolerance despite modification in dosage regimen
2. Malabsorption
3. Inability or unwillingness to take orally

- **Iron-dextran complex** or **iron sorbitol citrate** can be used Intra-muscularly or intra-venous route.

Dose (ml) = 0.0442 (desired Hgb – Observed Hgb.) X weight (Kg.) + (0.26 x weight Kg.)

B) Anemia of chronic diseases (ACD)

It occurs in association with a variety of chronic inflammatory and malignant diseases.

Etiologies

1) Chronic inflammatory diseases

a) **Infections** e.g. pulmonary abscess, TB, Osteomyelitis, pneumonia, bacterial endocarditis

b) **Non infectious**, e.g. Rheumatoid arthritis, SLE (systemic lupus erythematous) and other connective tissue diseases, sarcoidosis, Crohn's disease

2) Malignant diseases

E.g. carcinoma, lymphoma, sarcoma

Characteristic features are:

- NCNC or mildly hypochromic indices and red cell morphology
- Mild and non progressive anemia (Hgb rarely < 9.0g/dl) : Severity being related to severity of underlying disease
- Both serum iron and TIBC are reduced
- Serum ferritine is normal or raised and
- Bone marrow storage iron is normal but erythroblast iron is reduced

Pathogenesis is related to release of cytokines which mediate

- Decreased release of iron from macrophages to plasma,
- reduced RBC life span (~ 80 days) in effective erythropoiesis
- Inadequate erythropoietin response to anemia

Treatment of Anemia of Chronic Dideases:

1. Correction of underlying disease
2. Erythropoietin (40-80 % success rate)
3. Correction of reversible contributors (iron, folate, cobalamine supplements if necessary)

C) Sideroblastic anemia:

- Refractory anemia with hypochromia with ↑ marrow iron
- Many pathological ring sideroblasts are found in the bone marrow
- Is caused by defect in hem synthesis

Classification:

- Hereditary (sex linked recessive trait)
- Acquired

- Primary :Myelodysplasia
- Secondary :
  - Malignant diseases of the marrow
  - Drugs e.g. cycloserin alcohol, lead
  - Others: hemolytic anemia, megaloblastic anemia, malabsorption

~ 15% of marrow erythroblasts are ring sideroblasts in hereditary and 1^0 acquired forms.

Lead poisoning

- Inhibits both hem and globin synthesis
- Interferes with breakdown of RNA by inhibiting the enzyme pyrimidine- 5 nucleotidase $\Rightarrow$ accumulation of denatured RNA in red cells giving rise to **Basophilic stippling**.
- Hypo chromic/Hemolytic anemia with bone marrow ring sideroblasts
- Free erythrocyte protoporphyrin is raised

Management:

- Pyridoxine, folic acid therapy : may bring some response
- Repeated transfusion is ultimate choice

II. Macrocytic Anemia

Learning objectives: at the end of the student will be able to:-

1. *Define Megaloblastic anemia (MA)*
2. *Understand the pathogenesis of Megaloblastic anemia (MA)*
3. *List causes of Megaloblastic anemia (MA)*
4. *Compare and contrast various forms of MA*
5. *Identify the possible underling cause of Cobalamine deficiency*
6. *Understand the management of Megaloblastic anemia and asses response to therapy properly*

Megaloblastic Anemia and other Macrocytic Anemia

Pathogenesis: It's a descriptive morphologic term in which maturation of the nucleus is delayed relative to that of cytoplasm. The delay in maturation of the nucleus is attributed to defective DNA synthesis. This condition leads to Megaloblastic marrow and ineffective erythropoiesis.

The immature erythroblasts are destroyed within the bone marrow leading (Intramedulary hemolysis) which results *Megaloblastic anemia***.**

Etiologies of megaloblastic anemia

1. Vitamin B_{12} deficiency
2. Folate deficiency
3. Abnormalities of vitamin B_{12} or folate metabolism, transcobalamine deficiency, antifolate-drugs
4. Other defects of DNA synthesis: congenital enzyme deficiency, alcohol, treatment with hydroxyurea, etc.

Cells primarily affected are those with rapid turnover:

- Hematopoietic cells (RBCs, granulocytes, megakaryocytes)
- Cells derived from Respiratory tract and GIT etc

Macrocytic RBCs appear before the onset of anemia

Table VI-1-2 Difference in between Cobalamine and Folate physiology and daily requirement

Feature	***Cobalamine***	***Folate***
Source	Animal products (meat, diary product)	Vegetables, fruits and animal product
Daily requirement	2-5 µg	100 mg (50-200mg)
Body store	3-5(4) mg	5-20 mg
Time to develop anemia after the underlying cause for deficiency	3-4 years	4-6 months
Cooking	Little effect	easily destroyed
Plasma transport	Specifically bound by Transcobalamine (Tc. I, II, III)	2/3 easily bound to albumin, 1/3 is free
Usual therapeutic form	Hydroxocobalamine	Folic acid

Causes of Vit. B_{12} deficiency

1) ***Nutritional***: especially in vegans
2) ***Malabsorption***
   a) ***Gastric causes***
      i) Adult (addisonian) pernicious anemia
      ii) Congenital lack or abnormality of intrinsic factor
      iii) Total or partial gastrectomy
   b) ***Intestinal causes***
      i) Intestinal stagnant loop syndrome, jejunal diverticulosis, blind loop, stricture etc.
      ii) Chronic tropical sprue
      iii) Ileal resection and Crohn's disease
      iv) Congenital selective mal absorption with proteinuria
      v) Fish tapeworm : Diphlobotrium

Pernicious anemia:

Results from immunologic destruction of the Parietal cells in the stomach, which produce intrinsic factors, as in chronic atrophic gastritis, which results impaired production of intrinsic factors. Nearly 90% of patients show parietal cell antibody, 50% have type I or blocking antibody to intrinsic factor (IF) and 35% show type II or precipitating antibody to IF.

- MCV is increases
- Bone marrow : Hyper cellular and megaloblasts
- Peripheral film : neutrophilic hypersegmentation indicated by
  1 neutrophil with 7 segments
  2-3 neutrophils with 6 segments or
  > 5 neutrophils with 5 segments

To differentiate from folate deficiency biochemical tests should be done:

- Serum folate would be normal in patients given over-night dose or
- Determination of RBC folate level

Schilling test (3 phases) helps to identify the underlying cause of Vit.B_{12} deficiency.

1) Radioactive cobalamine is given orally + un labeled cobalamine intra muscularly (to saturate body needs). Then 24 hours urine cobalamine excretion is should be determined . Normally >8% should be excreted. If the excretion rate is < 8% , it may indicate malabsorption to Vit B_{12} .

2) Labeled cobalamine bound to IF is given orally

   In pernicious anemia Vit B_{12} absorption is corrected i.e. the daily urinary excretion rate is >8%

   In patients with abnormal in terminal ileum or pancreatic insufficiency Vit B_{12} absorption will not be corrected

3) Phase 2 repeated after 2 weeks of antibiotics
   - Vit B_{12} absorption is corrected in patients with bacterial over growth such as (blind loop syndrome)
   - Administration of pancreatic extract corrects pancreatic insufficiency.
   - Lack of/by pass of ileal intrinsic factor receptor (terminal ileal disease) or defective trans enterocyt cobalamine transport can't be corrected.

Treatment of megaloblastic anemia

1. ***Vit B12 Deficiency:*** is treated with Hydroxocobalamine which is given parentraly
   - **Dose: Initial dose:** 6 x 1000 µg over 2-3 weeks **and Maintenance :** 1000 µg every 3 months
   - ***Prophylactic therapy*** is indicated in patients with Total gastrectomy and Ileal resection
2. ***Folate deficiency:*** is treated with Folic acid preparation which is given orally
   - ***Dose***: 5 mg Po daily
   - ***Prophylactic therapy*** is indicated in pregnancy, sever hemolytic anemia, in patients with dialysis, and premature newborns
3. ***Additional measures:***
   - Correct underlying cause
   - Antibiotics for bacterial over growth and treatment of fish tapeworm

Response to therapy

- Feeling of general well being is restored in 48 hrs
- Reticulocytosis begins in 3-4 days and peaks in 7-10 days.
- If both folate and cobalamine deficiency present give cobalamine first

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Anemia, pages 586-624.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Anemia, pages 109-115.

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2. Leukemias

Learning Objective: At the end of this unit the student will be able to

1) *Define leukemia*
2) *Classify the different types of leukemias*
3) *Describe the possible etiologies and epidemiology of leukemia.*
4) *Identify the clinical features of leukemia*
5) *Make presumptive diagnosis and refer to hospitals where special investigations can be done*

Definition

- Leukemias are neoplasms of hematopoitic cells proliferating in the bone marrow initially and then disseminate to peripheral blood, lymph nodes, spleen, liver etc.
- Lymphomas differ from leukemias in that, lymphomas arise primarily from lymph nodes but spread to blood and bone marrow only in "leukemic phase" of the diseases.

Classification of leukemias - is based on

1. ***Cell of origin : there are*** two types of leukemias
    - Lymphoid leukemias
    - Myeloid leukemias
2. ***Clinical course of the disease*** - two forms of presentation of leukemias
    - Acute leukemias
    - Chronic leukemias

Thus, combining the above two criteria, there are have 4 main types of leukemias

A) ***Acute lymphoblastic leukemia (ALL)***
B) ***Chronic lymphoid leukemia (CLL)***
C) ***Acute myelogeneous leukemia (AML)***
D) ***Chronic myeloid leukemia (CML)***

Etiology

The etiologies of leukemias are unknown in most of the cases. But studies have demonstrated that both genetics and environmental factors are important in the causation of these diseases.

1. Genetics

- There is a greatly increased incidence of leukemia in the identical twin of patients with leukemia.

- Increased incidence of leukemia also occurs in people with chromosomal abnormalities such as Down's syndrome (trisomy 21).

2. ***Environmental factors like***

- ***Ionizing radiation***: The relation between acute leukemia and ionizing radiation, has been established in those having occupational radiation exposure, patients receiving radiotherapy and Japanese survivors of atomic bomb explosions. Radiation exposure increases the risk of CML, AML and ALL. No known relation with CLL.
- ***Chemicals*** like benzene, aromatic hydrocarbons, and treatment with alkylating agents and other chemotherapeutic drugs. Exposure to such chemicals is associated with increased risk of developing AML.
- ***RNA based retroviruses***

  Infection with HTLV - I is related to human T-cell leukemia & similarly Epstein Barr virus is related to ALL (T_3 subtype) and aggressive lymphoma.

Epidemiology

- Globally the incidence of all leukemias is 13/100,000/ year usually affecting men more than women.
- Certain leukemias are more common in a particular age group than the other, i.e. acute lymphoblastic leukemia (ALL) is common in children and young adults whereas AML, CLL and hairy cell leukemia are common in adults with peak between the 6^{th} & 7^{th} decade.
- A Study conducted in one of the teaching hospitals in Ethiopia has shown that leukemias were the commonest, accounting for about 35.5% of hematological admissions and acute leukemias were the leading cause of mortality, accounting for 78.1%of all hematological deaths.

Acute Leukemias

Acute leukemias are characterized by the presence of immature white blood cells in the marrow and peripheral blood.

There are two types of acute leukemias:

1. Acute lymphoblastic leukemia (ALL)
2. Acute myeloblastic leukemia (AML)

Such a classification of acute leukemias and further sub typing is done by using

- Morphology of the cells
- Immuno-phenotypic characteristics
- Cytochemical characteristics

Differentiation between ALL and AML is critical because the two have different

- Natural history
- Prognosis
- Response to treatment

A) Acute lymphoblastic leukemia (ALL)

Is common in children: 85 % of cases of ALL occur in children, and 90 % of leukemia that occur in children is ALL.

Lymphoblasts are abnormal white blood cells that are found both in the bone marrow & the peripheral blood of patients with ALL. They are characterized by

- Smaller size (10-15mm) than myeloblasts
- Thin rim of dark blue cytoplasm with no granules
- Nucleus is round or convoluted, and centrally located and has 1 or 2 nucleoli which are less prominent

Morphologically ALL is categorized into 3 subtypes (FAB classification)

1) **L_1** homogeneous population of small cells (childhood), a small nucleolus
2) **L_2** - more heterogeneous population of larger cells (more often seen in adults) with ≥ 1 prominent nucleoli
3) **L_3** - uncommon (constituting <5% of ALL), more mature subtype, large vesicular nucleus with basophilic often vacuolated cytoplasm.

Immuno phenotypic classification of ALL

1) **Common ALL** (L_1, L_2) account 75% of ALL, derived from precursors of B-cell.
2) **T-ALL** (L_1, L_2) account for 20%of ALL: common in adolescent males, associated with high WBC count, anterior, mediastinal mass and central nervous system involvement.
3) **B-cell ALL** (L_3) accounts for 5% ALL. Extramedullary presentation with metabolic abnormality.

B) Acute myeloblastic leukemia(AML)

Myeloblasts are abnormal cells that predominantly make up AML. These cells are larger than lymphoblasts and have:-

- Lower nuclear to cytoplasmic ratio
- Prominent multiple nucleoli
- Auer rods (stick like structures in the cytoplasm) in 50% of AML
- Granules in the cytoplasm

The FAB group divided AML into 8 subtypes based on

1. Degree of differentiation
2. Maturation of predominant cells towards granulocytes, monocytes erythrocytes or megakaryocytes

Subtypes of AML

1) M_0 (also called undifferentiated AML)
   - Composed of primitive cells without cytochemical stains
   - Account for 3% of AML
2) M_1 (AML without maturation)
   - Few if any azurophilic granules
   - Account for 20% of AML
3) M_2 (AML with maturation)
   - Blasts with promyelocytic granules
   - Auer rods present
   - Strong avidity to perixidase and Sudan black
   - Account for 25% of AML
4) M_3 (promyelocytic leukemia)
   - Hyper granular promyelocytes often with
   - Auer rods per cell
5) M_4 (Acute myelomonocytic leukemia)
   - Monocytoid appearing cells in peripheral blood.
   - Strong avidity to non-specific esterase
   - account for 20% of AML
   - M_5 (acute monocytic leukemia)
   - 2 subtypes

6) M5a – undifferentiated M5b - differentiated with 80% promyelocytes and monocytes
   - Both have avidity to non specific esterase and account for 20% of AML
7) M_6 (acute erythroleukemia)
   - Erythroblasts are more than 50% of all nucleated cells
   - Avidity to periodic acid Schiff stain
   - Account for 5% of AML
8) M_7 (acute megakaryocytic leukemia)
   - Megakaryoblasts are more than 30% of all nucleated cells
   - Account for 5% of AML.
   - Activity to PAS.

Pathophysiology

Acute leukemias are characterized by clonal proliferation of immature hematopoietic cells. The most important characteristic is a defect in maturation beyond the myeloblast or promyelocyte level in AML, and beyond lymphoblast in ALL. Proliferation of these immature cells in the bone marrow leads to

- Appearance of these blast cells in the circulation where they aren't normally seen and occlusion of microcirculation by blast cells (leukostasis)
- Infiltration of the tissues i.e. lymph nodes liver, spleen, skin, gum, viscera and central nervous system etc - causing enlargement of lymph nodes, liver, spleen, gum etc.
- Accumulation of blasts in the bone marrow has two major effects on the normal blood cell formation (hematopoisis) causing bone marrow failure.
  - They suppress the normal hematopoisis
  - They replace the normal elements in the bone marrow

  These bone marrow changes will decrease the normal blood cells in the circulation and cause
  - ***Infection*** - due to decreased WBC
  - ***Anemia*** - due to decreased RBC
  - ***Bleeding*** - due to decreased platelets

Clinical Features

ALL and AML share many clinical features. In the majority of cases the initial symptoms are present for less than 3 months and are the consequence of bone marrow failure, i.e.

- ***Symptoms of anemia*** such as tiredness, weakness, shortness of breath on exertion
- ***Recurrent infection*** of any part of the body is common due to
  - Low neutrophil count in the circulation

  - Functionally abnormal neutrophils
  - Disruption of mucosal barriers
- ***Bruising and/or bleeding*** related to low platelet count
- Occasionally, ***lymph node enlargement*** and/or symptoms relating to ***enlargement of the liver and spleen.***
- Symptoms related to hypoperfusion of the lungs and brain due to occlusion of microcirculation of these organs by blast cells.

Physical findings: but some patients may have

- Pallor
- Bruises, petechial hemorrhages, purpura
- Signs of infection like fever
- Peripheral lymphadenopathy in ALL, not common in AML
- Enlarged liver and spleen in ALL and small percentage of AML
- Testicular involvement in ALL (T. variant)
- Bone pain and sternal tenderness which are due to expanding malignant cell mass, occur in more than half of the patients with acute leukemias.
- Symptoms related to involvement of the central nervous system (meningitis, etc) and the kidneys.

Laboratory Investigation

The definitive diagnosis of acute leukemia is made on the basis of peripheral blood film and bone marrow aspirate examination. The following tests should be done to detect the disease & other associated abnormalities.

1) Complete blood count will show

- Hemoglobin -low
- WBC count -often very high, but occasionally decreased or normal
- Platelet count -low

2) Peripheral blood film shows characteristic leukemic cells, which are distinct from each other morphologically, i.e.

Table VI-2-1 Showing the main features of acute leukemic cells

	Lymphoblast	**Myeloblast**
Cell size	Smaller	Larger
Nucleus shape	Round , central	Irregular, eccentric
Nucleoli	1 or 2 in number and not prominent	More than two & prominent
Auer rods	absent	Present in 50%
Cytoplasm	Dark blue rim	Pale blue, granular

3) Bone marrow aspiration is mostly done on the sternum using a special needle and a smear prepared and stained with Wright stain , shows

- Increased cellularity with abnormal lymphoid or myeloid blast cell population.
- Replacement of the normal bone marrow elements

Management of acute leukemias

A) Chemotherapeutic agents, that have the capacity to kill leukemic cells, are used to treat leukemia.

Chemotherapy of acute leukemia's is divided in to four phases

a. *Remission induction* is characterized by intensive systemic chemotherapy with the goal of reducing leukemic cell below the level of clinical detection called complete remission.

b. Consolidation/ early intensification phase

After complete remission if there is no further treatment given, leukemia cells will expand and lead to relapse. In this phase intensive chemotherapy is given.

c. Maintenance phase here lower dose chemotherapy is given over several years.

d. Central nervous system prophylaxis in this phase local chemotherapy or radiation is given to sites of frequent relapse like CNS. This prevents leukemic meningitis.

Table VI-2-3. The treatment of acute leukemias (Cytotoxic drugs & phases of treatment).

Phase of treatment	ALL	AML
Remission induction	Combination of vincristine Prednisolone and L asparaginase Daunorubucin for 4 weeks	Daunorubucin+ cytosine arabinoside 4weeks (called 3+7 regimen
Continuation/intensification phase	Combination of 6-mercaptopurine & methotrexate+ Bone marrow transplantation	2-3 intensive cycles of the same as above or high dose of cytosine arabinoside+ bone marrow transplantation for young patients
CNS prophylaxis	Radiation to the whole brain Combined with intra-thecal methotrexate (given by lumber puncture)	No benefit because CNS relapse occurs only with systemic relapse. Therefore, it is not given.
Maintenance	oral 6 -mercaptopurine & Methotrexate	No benefit

B) Supportive treatment is applicable for both ALL & AML

b) For patients with severe anemia and thrombocytopenia (especially platelet count below 20,000 /ML with the risk of bleeding) may be transfused with whole blood and platelet concentrates.

c) Infections are common in acute leukemias.

Appropriate preventive measures should routinely be employed to prevent infections in such immunocompromised patients. These include

- Isolation of staff and visitors by the use of face masks
- Practice careful hand washing before coming in contact with the patient
- Advise the patient to eat only cooked foods

When infections occur, gram negative sepsis is the commonest presentation, which requires prompt evaluation and empirical antibiotic treatment until definitive diagnosis is made by blood culture, after which the antibiotic(s) can be modified depending on the organism identified & its drug sensitivity.

Chronic Leukemias

There are two main types of chronic leukemias

1) Chronic lymphocytic leukemia
2) Chronic myelocytic leukemia

C) Chronic lymphocytic leukemia (CLL)

Definition:

- It is an incurable disease of older people characterized by an uncontrolled proliferation and accumulation of mature B-lymphocytes (98% of CLL) and T-lymphocytes in rare instances.
- Although, the disease remains asymptomatic in a proportion of cases; symptoms of anemia, infections and bleeding resulting from bone marrow failure are common in the majority of patients at presentation.

Classification: FAB suggested 3 types of CLL

1. ***Typical CLL:*** - where more than 95% of lymphocytes in the blood are small lymphocytes.
2. ***Prolymphocytic CLL:-*** If ≥ 51% of lymphocytes in the blood are prolymphocytes
3. ***Atypical CLL*** :- if < 10% of lymphocytes in the blood are small lymphocytes

Clinical Features

In 25% the diagnosis is made incidentally in asymptomatic individuals when WBC count is done for other reasons. However, the majority will have signs and symptoms resulting from:-

1) tissue infiltration by leukemic cells
2) Bone marrow failure with peripheral blood cytopenias and immune suppression.

Symptoms

CLL is a disease of older adults and commonly present with

- Recurrent infections resulting from neutropenia & reduced immunoglobulin levels.
- Symptoms of anemia
- Painless lymph node enlargement
- Spleen and liver enlargement

Signs

- Anemia
- Enlarged lymph nodes, liver and/or spleen

Laboratory Investigation

1. ***CBC***
    - Hemoglobin is low or normal
    - WBC count > 15,000/mm^3 , of which 40% are lymphocytes, with a minimum of 5000/ mm^3 mature lymphocytes in the circulation
    - Platelets are low or normal
2. ***Bone marrow*** 30% of the cellular elements would be mature B cells
3. ***Serum immunoglobulins*** are low or normal
4. ***Coomb's test*** is positive in the presence of hemolysis.

Promyelocytic leukemia differs from the typical CLL described above in that the disease commonly present with

- Massive spleen enlargement but no lymphadenopathy
- Very high WBC count (> 200,000/L)
- Poor response to treatment
- The cells are B cells, but they are larger in size and have prominent nucleoli.

Staging of CLL

Clinical course of the disease is variable, and prognosis is correlated directly with the stage of the disease. There are two different staging classifications i.e.

1) RAI staging classification of CLL

Stage 0: Lymphocytosis only (in blood and bone marrow)

Stage I: Lymphocytosis with lymphadenopathy

Stage II: Lymphocytosis with liver and/or spleen enlargement

Stage III: Lymphocytosis with anemia (Hgb <11 gm/dl)

Stage IV: Lymphocytosis with thrombocytopenia (platelets < 100,000/ L)

Lymphocytosis is defined as WBC count > 15,000/ L, of which 40% are lymphocytes

2) Binet staging classification of CLL

Stage A = < 3 involved lymphoid areas Hgb>10g/dl

Stage B= >3 involved lymphoid areas Platelets < 100,000/ L

Stage C = Any number of involved Hgb < 10 g/dl and/or Platelets < 100,000/ L
lymphoid areas

NB: The cervical, axillary and inguinal lymph node groups (unilateral or bilateral), the spleen and the liver each counted as one area.

Prognosis

- Stage 0 and 1 CLL has good prognosis. If a patient has stage 0 disease without other poor prognostic factors, the median survival would be more than 10 yrs without treatment.
- Stage II has Intermediate prognosis - median survival is 5 yrs
- Stage III and IV has worse prognosis - Median survival is 3 years

Treatment

Patients with CLL should be referred to centers where they can be treated and followed.

The disease may remain stable for several years without treatment. Therefore, no advantage in starting drugs before there is any clinical indication for treatment:

Indication for initiating treatment include:

1) Hemolytic anemia
2) Cytopenias (neutropenia, thrombocytopenia, etc) with recurrent infections, bleeding
3) Disfiguring lymphadenopathy
4) Symptomatic organomegally
5) Marked systemic symptoms
6) Advanced disease

When treatment is required alkylating agents are often the drugs of choice:

1) Chlorambucil: is given as small daily doses or larger pulse (intermittent) every 3-6 wks **or**

2) Cyclophosphamide is also used in the same way (daily or pulses)

3) Steroids (prednisolone) can be used in CLL if the patient develops autoimmune hemolytic anemia, autoimmune thrombocytopenia etc

Other modalities of treatment which are rarely employed include

- Combined chemotherapy (similar to lymphoma) is used for advanced disease
- Splenectomy/splenic irradiation
- IV immunoglobulin for life threatening infection

Response to treatment can be assessed by

- Declining WBC count
- Increase Hgb, platelet count
- Decrease size of Lymph nodes

D) Chronic Myelocytic Leukemia (CML)

Definition: It is disease of older adults and characterized by clonal expansion of hematopoitic cells of myliod origin, possessing *Philadelphia chromosome*. It has a progressive clinical course with three phases starting with chronic phase and evolving to accelerated phase and then to blast transformation.

Epidemiology

The incidence of CML is 1.3/100,000 population /year, with men more affected than women, increasing slowly with age until middle forties when the incidence rises rapidly.

In the majority of cases the etiology is unknown. However, CML has been one of the leukemias observed to have an increased prevalence following atomic explosion at Hiroshima and Nagasaki.

Clinical Features

The clinical features of CML depend on the stages of the disease, and range from early asymptomatic phase to severe manifestations of the accelerated phase and blast transformation. Therefore, manifestation can be described as follows:-

1. ***Chronic Phase:***
    - The onset is insidious and some patients can be diagnosed while asymptomatic during health screening visits.
    - Others may present with fatigue, anemia, night sweating, fever, weight loss and symptoms related to enlarged spleen i.e. left upper abdominal dull pain and early satiety.
    - A few cases may show symptoms related to granulocytic or platelet dysfunction i.e. recurrent infections and thrombosis manifesting commonly with persistent painful erection of the penis (priapism) and cerebrovascular accidents.

2. Accelerated phase and blast transformation(or blast crisis)

With progression of CML from chronic phase to accelerated phase and then to blast transformation patients will present with severe symptoms such as

- Unexplained fever
- Progressive weight loss
- Bone and joint pain
- bleeding/ thrombosis
- Recurrent infections
- Increasing dose requirement of the drugs used for controlling the disease
- 10-15% of patients may present for the first time with either the accelerated phase or blast transformation.

Physical examination may show

- In the early stage 90% of or more of the cases may show
  - Moderately pale conjunctivae
  - Enlarged spleen and mild liver enlargement.
- Late in the disease process patients may develop
  - Lymph node enlargement
  - Chloromas – leukemic deposits on the skin &
  - Tender sternum

Laboratory Findings

1) WBC count is increased of the granulocytic series with variable degrees of maturity i.e. mature neutrophils and band forms are seen in the peripheral blood film. Moreover immature granulocytes such as promyelocytes, myelocytes and metamyelocytes are seen in the peripheral film with increased number. Some myeloblasts are also seen, and the percentage of blasts varies according to the stage of the disease, i.e.

- ***Chronic phase***: blasts account for < 5% of granulocytes in the blood
- ***Accelerated phase***: blasts account for ≥ 15% but < 30% of granulocytes in the blood
- ***Blast crisis:*** blasts account for ≥ 30% granulocytes in the blood

Phagocytic function is normal at diagnosis and remains normal in the chronic phase.

Basopilia and monocytosis are commonly observed in the accelerated phase & blast transformation.

2) ***Patelet count*** is elevated
3) ***RBC count*** and ***hemoglobin concentrations*** are low, presenting with anemia
4) ***Bone marrow*** aspiration: shows increased cellularity primarily of the myeloid and megakaryocytic lineage, but percentage of marrow blasts remains normal or slightly increased

Depending on the laboratory findings the three stages can be defined as follows:-

Chronic Phase

- <5% of circulating blasts
- < 10% blasts + promyelocytes in the blood
- Platelets are increased
- Mild anemia
- Increased cellularity of bone marrow with normal or increased percentage of blasts.

Accelerated Phase

- Worsening anemia
- Blasts 15-30% of granulocytes (in the blood or bone marrow)
- Blasts and promyelocytes ≥ 30% of granulocytes (in the blood or marrow)
- Basophils ≥ 20% of granulocytes
- Platelet counts < 100,000/L

Blast Crisis

- Blasts ≥ 30% of granulocytes (in the blood or marrow)
- Hyposegmented neutrophils

Blast cells may be

- Myeloid in 50% (AML)
- Lymphoid in 30% (ALL)
- Erythroid in 10% (erythroleukemia)
- Undifferentiated in 10%

Treatment

- The goal of treatment is complete molecular remission and cure (i.e. achieving prolonged, durable non-neoplastic and non clonal hematopoisis).
- The treatment includes the following (used singly or in combination)
  1) Chemotherapy - hydroxyurea or busulphan - used in Ethiopia
  2) Bone marrow transplantation - the only curative treatment but not available in this country

3) Interferon treatment

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Acute and chronic Myeloid leukemia, Malignancies of Lymphoid cells, pages 631-655.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Acute leukemia, 123-126.

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3. Lymphomas

Learning objectives: At the end of this lesson, the student will be able to:-

1. *Define lymphomas*
2. *Understand the differentiating features of common lymphomas*
3. *Identify clinical features of lymphomas including specific features*
4. *Understand the clinical staging of lymphomas with its significance*
5. *Principles of management of lymphomas*

Definition: Malignant transformation of cells residing predominantly in lymphoid tissue.

Lymphoma is broadly classified as

- Hodgkin's disease
- Non-Hodgkin's lymphomas

A. Hodgkin's disease

Epidemiology:

- It has bimodal age incidence (20-30 years and > 50 years).
- In developing countries young adults are commonly affected.
- Male to female ratio = 2:1

Clinical manifestations

- Most patients present with non-tender asymmetrical, firm, discrete and rubbery enlargement of superficial nodes: Cervical (60-70%), axillary (10-15%) inguinal (6-12%). Has waxing and waning feature.
- Mild spleenomegaly (50%), mediastinal Lymphadenopathy (6-11%) with or without plural effusion and superior venacaval syndrome may be present.
- Constitutional symptoms like fever, weight loss and sweating are common in widespread disease. Fever is found in 30% of patients, and it described as Pel – ebsteins fever characterized by weeks of febrile period, interspersed by several weeks of afebrile period.
- Pruritis is seen in 25%of patients
- Alcohol induced pain in the affected area

- Others symptoms include Weight loss, profuse sweating, weakness, fatigue, anorexia, cachexia

Hematological findings

- Normocytic normochromic anemia
- 1/3rd of patients may have leukocytosis
- Eosinophila
- Lymphopenia may be found in advanced disease
- Platelets count is variable (normal or increased in the early stage and decreased in the late stage)
- ESR is elevated
- Bone marrow involvement – late in the course

Immunologic findings

- Progressive loss of immunologicaly competent T-lymphocytes leads to impaired cell mediated immunity which increases susceptibility to viral infections (herpes zoster, CMV) and fungal infections (e.g. Cryptococcus and Candida) infections . Moreover patients will have increased risk of reactivation of latent Tuberculosis infection.

Biochemical findings

- $\uparrow Ca^{2+}$, $\downarrow Po_4^{-3}$, $\uparrow$Alkaline Phosphatase, $\uparrow$LDH indicates poor prognosis
- Hyperuricemia,$\uparrow$ Transaminases and $\uparrow$ bilirubin.

Diagnosis

- Lymph node biopsy: histological examination of an excised lymph node.
- Feature: the distinctive multinucleated, polyploidy cell with a characteristic **Owel- eye** appearing ***Reed-Stern berg*** **(RS)** cells on an appropriate inflammatory background.

Classification

Histologically Hodgkin's disease is classified in to four groups.

These are listed depending on worsening order of prognosis as follows:

1. ***Lymphocytic predominant***
2. ***Nodular sclerosis***
3. ***Mixed cellularity***
4. ***Lymphocytic depleted***

Clinical staging

Stage 1: Only affecting one lymph node area

Stage 2: 2 or more lymph node areas on the same side of the diaphragm involved

Stage 3: Disease involving lymph nodes above and below diaphragm; splenic involvement is included here.

Stage 4: Extra-nodal site involvement (Liver, bone marrow and other extra nodal sites)

Depending on the presence or absence of constitutional symptoms the stages are further classified as A (no constitutional symptoms) and B (presence of constitutional symptoms.)

Treatment

1. **Radiotherapy** – mainstay for stage I and II diseases; used for stage III and IV **with chemotherapy**.
2. **Chemotherapy**
   - Cyclical chemotherapy for stage III and IV diseases
   - In stage I and II patient with bulky disease

     E.g. - Mediastinal widening by 1/3rd

     Lymph node > 10 cm in diameter

The commnly used combinations of chemotherapy include

- MOPP: mustine, vincristine (oncovine), procarbatine, predinisolone
- ABVD : adramycin, bleomycine, vinblastin, decarbazine
- This combination therapy is either used alone or MOPP – ABVD hybrid given for 6 cycles (or 4 cycles after full remission).

3. **Relapse cases are** better treated with autologous Bone marrow transplantation with total body irradiation and high dose chemotherapy.

Prognosis – depends on stage

Five-year survival being

Stages I and II: 85%

Stage III A: 70%

Stages III B & IV: 50%

B. Non Hodgkin's Lymphoma (NHL)

Predisposing diseases/ factors to NHL

- In HIV infected patients there is an increased incidence of lymphoma often at unusual sites like CNS; usually B-cell origin with high or intermediate grading.
- Immunosuppression increases the risk of developing NHL
- Others : Celiac disease, dermatitis herpetiformis and angioimmunoblastic LAP predispose to T-cell lymphomas
- Infections: e.g. *Helicobacter infection* is associated with ↑ frequency of MALTOMAS
- Autoimmune diseases may cause NHL

Clinical features

- Superficial lymphadenopathy with a classic triangular distribution (the three vertexes ling over the cervical and the two epitrochlear lymph nodes, while the base lies over abdominal organs and lymph nodes.)
- Constitutional symptoms are encountered less commonly when compared with HD and if present indicates dissemination.
- Oro-pharyngeal involvement is seen in 5-10% cases: have involvement of Waldeyer's ring including the tonsils adenoids and paratonsilar areas
- Anemia, neutropenia (infection) and thrombocytopenia may follow - bone marrow involvement or may be autoimmune in origin
- Abdominal organs and lymphnode involvement is more common in NHL than HD
- Other organs: skin, brain, testis, GIT, or thyroid involvement is frequent.

Laboratory findings:

1) ***Hematological findings***
   - Normocytic normochromic anemia due to autoimmune hemolytic anemia
   - Cytopenias or leukoerythroblastic features
   - Lymphoma cells in may be seen in the peripheral blood sometimes
   - Bone marrow biopsy may show focal or diffuse involvement
2) ***Immunologic markers*** are used for classification
3) ***Chromosomal findings:*** various forms of translocations identified

Blood chemistry

- Uric acid level is elevated
- Liver enzymes are abnormally elevated

- LDH ↑ (in rapidly proliferating and extensive disease hence has prognostic implication.)

Prognostic features:

- Histology
- Staging
- Age > 60 years – unfavorable
- Poor performance status
- Multiple sites of extra nodal involvement
- ↑ LDH
- Bulky disease (mass > 5 cm in diameter)
- Prior history of low grade disease
- AIDS or other causes of imunosupression related

Treatment

Low – grade malignancy:

No need of treatment if the patient is asymptomatic

1) **Local radiotherapy** is indicated for stage **I**, **Iε** or stage **II**
2) **Combination chemotherapy** for advanced cases

   Chlorambucil or *cyclophosphamide* or repeated courses of *fludarabine*
3) BMT (bone marrow transplantation)
4) INF - α

Intermediate – grade malignancy

Localized disease

Initial combination therapy with **CHOP** (cyclophosphamide, Hydroxodunorubicin (Adriamycin), Vincristine (oncovin) and prednisolone) **followed by irradiation**.

Disseminated diseases: Combined Chemotherapy is the treatment of choice.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Malignacies of Lymphoid cells, pages 641-655.

4. Disorders of Hemostasis

Bleeding Disorders

Learning objectives: at the end of this topic students are expected to:-

1. *Know common causes of hemiostatic disorders*
2. *Differentiate clinically between primary and secondary hemiostatic disorders*
3. *Know possible causes of thrombocytopenia*
4. *Know clinical approach to a patient with thrombocytopenia*
5. *Understand how to approach a patient with drug induced thrombocytopenia*
6. *Be able to recognize cases of ITP and refer to an appropriate set up*
7. *To be introduced with some of vascular causes of bleeding*
8. *Know commoner causes of coagulation abnormalities with their peculiarity and similarity*

Abnormal bleeding may be due to:-

1. ***Primary haemostatic disorders*** **:** bleeding disorders resulting form either platlet or vascular abnormalities
   - Vascular disorders
   - Thrombocytopenia
   - Functional platelet defect
2. Secondary haemostatic disorder : resulting from problem in the coagulation pathway
   - Defective coagulation

1) Disorders of the platelet and vessel wall (primary haemostatic disorders)

- Patients with platelet or vessel wall disorders usually bleed in to superficial sites such as the skin, mucous membranes, or genitourinary or GI tract.
- Bleeding begins immediately after trauma, and either responds to simple measures such as pressure and packing or requires systemic therapy with glucocorticoids, desmopressin, plasma fractions and platelet concentrate.

Common platelet vessel wall disorders are:

- Thrombocytopenia
- Von willebrand's disease (VWD)

- Drug induced platelet dysfunction

Platelet Disorders

- Platelets are produced from fragmentation of megakaryocytes in the bone marrow results in platelets of which 1/3 sequesters in the spleen, 2/3 circulates for 7-10 days.
- Platelet count in a normal adult ranges from 150,000 – 450,000/ml.
- When platelet count is reduced there will be reactive marrow megakaryocytosis
- Platelet count varies during menstruation i.e. rises during ovulation and failing during the onset of menses.
- It is also Influenced by nutritional state: decreased in sever fe^{2+}, folic acid, or vitamin B_{12} deficiency.
- Platelets are acute phase reactants hence may be increased in patients with systemic inflammation, tumors, bleeding and mild iron deficiency hence the term secondary or reactive thrombocytosis is used. It is mediated by cytokines IL-3, 6, and 11.

Thrombocytopenia: May follow any of the following three mechanisms

- Decreased bone marrow production
- Increased splenic sequestration or
- Accelerated destruction of platelets

To determine the etiology one should do

- Careful examination of peripheral morphology
- Assessment of marrow morphology by examination of an aspirate or biopsy
- An estimate of splenic size by bed side palpation supplemented by ultrasonography.

Impaired production of platelets:

- Is commonly associated with stem cell injury
- Affect multiple hematopoietic cell lines, hence there is varying degree of accompanying anemia and leucopoenia
- Bone marrow aspirate or biopsy show reduced number of megakaryocytes

Common causes are:-

- Marrow aplasia
- Fibrosis or
- Infiltration of the marrow with malignant cells

Less commonly**:**

- Cytotoxic drug use
- Rarely congenital megakaryocytic hypoplasia and thrombocytopenia

Splenic sequestration: usually follows conditions causing spleenomegaly such as

- Portal hypertension
- Spleenic infiltration with tumor cells as in myeloproliferative disorders or lympho proliferative once)

Accelerated destruction:

- **Non immunologic**:- associated with abnormal vessels, fibrin thrombi and heart valve prosthesis
  - Vasculitis, hemolytic uremic syndrome, TTP,
  - DIC
- **Immunologic:** platelets coated with antibody, immune complexes, or compliments are rapidly cleared by mononuclear phagocytes in the spleen or other tissues; may follow viral or bacterial infections, drugs, etc
- **Drug – induced thrombocytopenia**

Drugs that may cause thrombocytopenia

- Chemotherapeutic agents – especially carboplatin, alkylating agents, anthracyclines, antimetabolites
- Antibiotics – sulfonamides, penicillines, cephalosporines
- Heparins – Highest incidence is with unfractionated products
- Cardiovascular agents – Thiazide diuretics, rarely angiotensine converting enzyme inhibitors

- Most drugs induce thrombocytopenia by eliciting an immune response in which platelets are innocent bystanders. The best proof of drug induced thrombocytopenia is prompt rise in the platelet count when the suspected drug is discontinued
- Most recover within 7-10 days of discontinuation, some with platelet count of 10,000 to 20,000/ml may have sever hemorrhage and hence need temporary support with glucocorticoid, plasmapheresis, or platelet transfusion; and patents should be instructed to avoid the offending drug in the future.
- Heparin induces a paradoxical white thrombus formation leading to consumptive thrombocytopenia.

Idiopathic /Immunologic Thrombocytopenic Purpura

Immunologic thrombocytopenias are divided on the basis of the pathologic mechanism, the inciting agent, and the duration of the illness. Accordingly they are classified as acute and chronic.

Acute ITP:

- Usually follows viral upper respiratory infection common in children aged 2-6 yrs (accounts for 90% of pediatric cases)
- 60% recovers in 4 to 6 wks and > 90% recover within 3 to 6 months.

Chronic ITP:

- It is common in adults and run a more indolent course.
- Women age 20 – 40 are afflicted most commonly and outnumber men by a ratio of 3:1.
- It presents acutely or more often with prior history of easy bruising and mennometrorhagia.
- There is immune mediated platelet destruction as well as functional platelet dysfunction.

Investigation

- Platelet count, complete blood count, serology for HIV, screening for SLE
- Bone marrow aspirate to look for reactive thrombocytosis (increased megakaryocytes)
- Ultrasonography of the abdomen to look for spleenomegaly

NB- HIV infection is common cause of immunologic thrombocytopenias in young adults.

Treatment:

It depends on age, severity, and anticipated natural history.

Specific treatment may not be necessary unless platelet count is < 20.000/ml

1) Steroids :

- Symptomatic patients with chronic ITP are placed on prednisone 60 mg/day for 4 to 6 wks; then tapered slowly over another few weeks.
- Those patient who fail to maintain a normal platelet count after a course of steroid are eligible to splenectomy (steroid responsive but dependent patients are most likely to respond to splenectomy)

2) ***Intravenous immunoglobulines (IVIG)*** or anti-Rho (win Rho) (reserved for those with sever thrombocytopenia and clinical bleeding who are refractory to other measures)
3) ***Platelet transfusion*** is considered only in those with eminent CNS bleeding as a temporary measure.
4) ***Emergency splenectomy*** (for those who are desperately ill and refractory to medical measures)
5) ***Antiretroviral treatment*** for those dually infected with HIV increases platelet count.

NB: Failure to respond to splenectomy may signify presence of accessory spleen which may be evidenced by peripheral blood smear examination for *Howell jelly body* which appears in the circulation of asplenic patients. Such patients may need Immunosuppressive therapy or Plasmapheresis.

Vascular bleeding disorders

1) ***Hereditary hemorrhagic telangiectasia*** : is an autosomal dominant disorder
2) ***Acquired vascular defects:***
   - **Simple easy bruising**: benign disorder seen in women of child bearing age.
   - **Senile purpura**: due to atrophy of connective tissues of cutanous vessels
   - **Purpura associated with infection**: follow vascular damage by infecting organs or immune complex deposit e.g. meningococcemia, dengue fever.
   - **Henoch – Schonlein's syndrome**: is immune complex (type III) hypersensitivity. Is characterized by purpuric rash on the buttock and extensor surfaces; abdominal pain; painful joint swellings; hematuria. It is usually self limiting; however, some times may cause renal failure.

2) Coagulation Disorders (Secondary Hemostatic Disordrs)

- Hemophiliac A
- Hemophiliac B
- Von will brand's disease

Hemophilia A (hemophilia)

- Commonest hereditary disorder
- Sex linked but 33% may not have family history and results from spontaneous mutations.

Defect: Absence or low level of plasma factor VIII

Clinical feature

- Profuse post circumcision hemorrhage in infants;
- Recurrent painful hemarthroses and muscle hematomas
- Spontaneous intracerebral hemorrhage is important cause of death
- Transfusion related disorders: Hepatitis (HBV, HCV) and HIV infection are frequent complications of repeated Coagulation factor transfusions.

Table VI-4-1: Correlation of coagulation factor activity and severity in hemophiliac and factor IX deficiency

Coagulation factor activity(% of normal)	**Clinical manifestation**
< 1	Sever disease Frequent spontaneous bleeding Episode from early life Joint deformity and crippling
1-5	Moderate disease Post traumatic bleeding Occasional spontaneous episodes of bleeding
5-20	Mild disease Post-traumatic bleeding

Diagnosis

1) Typical clinical presentation
2) Activated partial thromboplastin time(APTT)
3) Factor VIII clotting assay

Treatment:

Factor VIII replacement or treatment with Desmopressin.

Spontaneous bleeding is usually controlled if patient's factor VIII activity is > 20%.

For major surgery or serious post traumatic bleeding or hemorrhage occurring in dangerous sites Factor VIII level should be raised to 100% and maintained above 60% until healing occurs.

Unit of Factor VIII needed can be calculated by the following formula:

X = % rise in factor VIII x weight (kg)

K

Where K = 1.5 for Factor VIII,

= 1 for Factor IX and 2 for Factor XI; 1 unit of Factor VIII = 1% VIII activity

Table VI-4-2. Comparison between different coagulation disorders

Features	**Hemophiliac**	**Factor IX deficiency**	**Von willi brand's disease**
Inheritance	Sex linked recessive	Sex linked recessive	Autosomal dominant
Site of bleeding	Body cavities, joint & intramuscular spaces	Body cavities, joint & intramuscular spaces	Both mucocutaneous & other mentioned sites
Platelet count	N	N	N
Bleeding time	N	N	Prolonged
Prothrombin time (Pt)	N	N	N
partial thromboplastine time (PTT)	Prolonged	Prolonged	Prolonged or normal
VIII	Low	Normal	Low
VWF	Normal	Normal	Low
Factor IX	N	Low	Normal

Von will brand's disease

- Has both functional platelet abnormality (abnormal platelet adhesion) and low factor VIII activity
- Inheritance is autosomal dominant with variable degree of penetrance.
- Defect is reduced synthesis of VWF which facilitates platelet aggregation and carrier of Factor VIII (protecting it from premature destruction**).**

Treatment:

- Intermediate – purity F VIII concentrates (containing both F VIII and VWF)

- Desmopressin

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Disorders of Hemostasis, pages 673-694.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Disorders of hemostasis and coagulation, pages 127-136.

CHAPTER SEVEN
DISEASE OF METABOLISM AND ENDOCRINE SYSTEM

1. Introduction to Diseases of the Endocrine System

- Like the nervous and the immune systems the endocrine system main function is being a media of intercellular communication for a proper function of the body.
- This is achieved by organic compounds called hormones. Hormones are directly released into the blood therefore are said to be produced by “ductless glands”. Some hormones are bound to carrier proteins for transport but it is the free form that is physiologically active. These hormones first bind to plasma membrane of the target cells’ receptors .Then a series of cascade reactions (biochemical reactions that initiate and accelerate themselves which are mediated by cyclic AMP) or by direct enzyme induction on the nucleus should occur before the nucleus of the cells is influenced to send a command for an action.
- The release of hormones is controlled by feedback of serum level but also the physiologic, morphologic and biochemical effects of hormones could play a role.
- These hormones are finally inactivated in target tissues with the exception of thyroid and insulin which are degraded in the liver and kidneys as well.
- The state of endocrine function is evaluated by level of hormone or the metabolic effects of the hormone. With few rare exceptions both high and low levels of hormone result in disease.

  E.g. High level of thyroid hormone results in hyperthyroidism while a low level of hormone results in hypothyroidism.
- Endocrine functional assessment is very important in clinical practice but with serious challenge for resource limited nations like ours. Hormone levels are too low making routine laboratory determination difficult and as a result very sensitive assay are needed which are not routinely available due to expense and special expertise needed.
- The other challenge result from the very nature of pattern of hormone secretion during the day making it necessary to take samples at specific times of the day or doing interventions to suppress or stimulate hormone production whenever the levels are border line for decision making.

Homeostasis

Feed back control, both negative and positive, is a fundamental features of endocrine system. Each of the major hypothalamic –pituitary hormone axes is governed by a negative feedback, a process that maintains hormonal levels within a relatively normal range.

The Hypothalamus

The hypothalamus produces different releasing hormones that stimulate the pituitary gland.

- *TRH stimulate the production of TSH*
- *CRH stimulate the production ACTH*
- *GnTH stimulate the production LH/FSH*
- *GHRH stimulate the production GH*

The hypothalamus is affected by negative (inhibitory) feedback from the pituitary gland as well as from serum level of different hormones or their metabolic effect.

The hypothalamus produces antidiuretic hormone (ADH) which participates in control of fluid and electrolyte and Oxytocin which participate in uterine contraction after delivery. These two hormones are released in the posterior part of the pituitary gland.

The pituitary gland produces trophic hormones that stimulate the peripheral endocrine glands.

- Thyroid stimulating hormone(TSH) stimulates the thyroid gland to produce T_3 and T_4
- Adrenocorticotrophic hormone (ACTH) stimulates the adrenal cortex to produce cortisol.
- Luteinizing hormone (LH)/Follicular stimulating hormone stimulate the ovaries or the testis.
- Growth hormone is also produced by the anterior pituitary and influence body growth
- Prolactin is also produced by the anterior pituitary and influence lactation in females.

The peripheral glands produce specific hormones:

- The thyroid glands produce Thyroid hormone (T_3 and T_4)
- The adrenal glands produce Cortical
- Ovary and testes produce hormones that control sexual activity and reproduction.

Other endocrine organs

- Pancreas: produces insulin and glucagon
- Liver: produces somatostatin
- Kidneys: produce : renin, angiotensin, erythropoietin, Vit-D
- Stomach: produce gastrin

The target cells execute the command delivered by hormones.

2. Diabetes Mellitus

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define Diabetes Mellitus*.
2. *Describe the pathophysiology of* Diabetes *Mellitus.*
3. *Understand the epidemiologic significance of Diabetes Mellitus.*
4. *Understand the different types of Diabetes Mellitus.*
5. *Identify the clinical manifestation of Diabetes Mellitus.*
6. *Understand the diagnostic approach of Diabetes Mellitus.*
7. *Identify acute and chronic complications of Diabetes Mellitus.*
8. *Manage patients with acute complications Diabetes Mellitus*.
9. *Understand the prevention of chronic complications of Diabetes Mellitus*
10. *Understand the course and prognosis of Diabetes Mellitus*.

Diabetes Mellitus: is a common endocrine disorder characterized by:

- *Hyperglycemia*
- *Manifesting often with symptoms and signs of osmotic diuresis such as polyuria and polydypsia*
- *Calorie loss, generalized weakness, polyphagia and weight loss.*

Resulting from either an absolute deficiency (Type 1) or a relative deficiency (Type 2) of the hormone, Insulin.

- These disorders are associated with reversible and acute complications such as ketoacidosis, which becomes fatal if treatment is delayed.
- Disabling chronic complications affecting vision, kidneys, the nerves the vessels and the heart are common in those who are diagnosed very late, or in those who are not on proper medical follow up and care.

Etiology and Classification:

Type 1 DM (formerly known as insulin-dependent DM)

- Usually occurs in childhood or early adulthood (age less than 30)
- Patients are usually thin.

- They require insulin for survival and develop ketoacidosis when patients are not on adequate insulin therapy.
- This accounts for 10% of cases of DM.
- Oral hypoglycemic agents will not be effective to lower the blood glucose level.
- Type 1 DM is due to β-cell destruction, with absolute deficiency of insulin, which is of multifactorial causes such as genetic predisposition, viral and autoimmune attacks on the beta islet cells. It may be immune mediated or idiopathic**.**

Type 2 DM (formerly non insulin-dependent DM)

- Usually occurs in people >40 years of age
- Most (about 60%) of the patients are obese.
- Type 2 DM occurs with intact beta islet cell function but there is peripheral tissue resistance to insulin.
- There may be some decrease in insulin production or a hyperinsulin state.
- These patients are not prone to develop ketoacidosis but may develop it under conditions of stress.
- Patients do not require insulin for survival at least in the earlier phase of diagnosis.
- The blood sugar level can be corrected by oral hypoglycemic agents.

Other specific types

A. Genetic defects of β-cell function: MODY 1 , MODY 2 , MODY 3 etc
B. Genetic defects in insulin action : Type A insulin resistance , Lipodsytrophy syndromes
C. Diseases of the exocrine pancreas: Chromic pancreatitis , Pnactreatectomy , hemochromatosis
D. Endocrinopathies : Cushing's syndrome, pheochromocytoma , acromegaly
E. Drug- or chemical-induced DM (beta-blockers, oral contraceptives , glucocorticosteriods

Gestational onset DM (GDM): is when diabetes onsets during pregnancy and resolves with delivery. These patients are at a higher risk for developing DM at a later date.

Epidemiology

- Globally 124 million people are said to be affected by DM, of which 97% are type 2 cases.

- In USA 1 to 2% of the general population has abnormal fasting blood sugar level, and 20% of above 60 years have diabetes.
- In Asia, particularly urban India, prevalence DM has climbed to 11%, while in South African urban Indians it is as high as 18%.
- Amongst Pima Indians in America the prevalence of DM is very high (up to 50%) making genetics predisposition an important factor.
- Africa is not free from this disease which traditionally is considered the disease of the affluent societies of the first world. In Tunisia the prevalence of DM is 4%, in South Africa 5%, in Tanzania 0.9%.
- In Ethiopia one community based study showed that the prevalence of DM in Gondar area of northern Ethiopia was found to be about 0.5%, and about 4.7% among older than 40 years.
- Emigrants from Ethiopia to Israel have shown a higher prevalence of 8.9%.These findings imply that the incidence of disease increases with increasing age, as well as either the dietary habit or sedentary and stressful life style of the developed countries.

Mechanism of Disease in Diabetes Mellitus

Insulin is produced by the β-cells in the islets of Langerhans in the pancreas. Insulin secretion is stimulated by amino acids and parasympathetic nerves. It is inhibited by glucagon.

The Biochemical actions of Insulin include:

- Switches off hepatic glucose production (inhibits Gluconeogenesis)
- Increase uptake and utilization of glucose by muscle
- Inhibits lipolysis and by doing so prevents ketogenesis.
- Enhances uptake of amino acids into muscle for protein synthesis and inhibition of breakdown of proteins

Mechanism of disease in Type 1 Diabetes

Type 1 diabetes mellitus is believed to be due to autoimmune destruction of beta cells.

- The triggering agent (i.e. - a viral infection) will expose these cryptic (hidden) self antigens to which the immune system has not developed tolerance. Therefore an autoimmune process is set-up destroying self tissue, in this case the beta cells of the islets of Langerhans.
- The other mechanism of injury is molecular mimicry between trigger antigen (virus) and β-cell antigen. or instance Coxsackie virus antigen and that of glutamic acid

decarboxylase (GAD) found within the β-cells has similar chemical structure, so that the antibodies produced to fight the foreign antigen of the virus also cross react with antigens of self tissue bearing GAD hence destroying it .

Natural history of type 1 diabetes

- The disease is progressive going through phases of antibody production, then phase of impaired GTT followed by an abnormal FBS, and finally culminating in an abnormal FBS with Ketonemia.

Honeymoon period:

- In young people who are diagnosed for the first time to have overt DM, the DM may have been precipitated by acute metabolic stressful conditions (such as infection or pregnancy). In such circumstances, the increased metabolic demand for insulin, may lead to a relative insulin deficiency, and patients become symptomatic, and may need exogenous insulin to control their symptoms.
- With the return to baseline metabolic demands, when the stressful event abates, the pancreatic reserve may be adequate to maintain normal or near-normal blood glucose. Such patients may undergo a period of transient "cure" during which time they may not require exogenous Insulin to control their blood glucose level. Because of this, such patients are said to be in a "**HONEYMOON**" period.
- This is unfortunately is transient and the patients will be needing insulin again when the progressive destruction of β-cells leads to absolute insulin deficiency.

Mechanism of Type 2 disease:

- In Type 2 DM insulin resistance plays a central role in the pathogenesis.
- In obesity, increased production of non-esterified fatty acids, leads to resistant of peripheral organs to insulin which leads to increased gluconeogenesis in the liver, and decreased peripheral uptake and utilization of glucose by muscles .
- Initially there is hypersecrtion of insulin by β-cells, to overcome the insulin resistance. But later on β-cells fail to respond to the level resistance. Then β-cell number is decreased and amyloid is deposited in islets.

Predisposing factors for Type 2 DM

1) ***Genetic Predisposition*** plays an important role. The evidences are :-
   - Concordance among identical twins is upto100%
   - Concordance among fraternal twins is 20%
   - Familial aggregation history is common and up to 50% of siblings and 33% of children of diabetics develop diabetes.
2) ***Environmental factors :***
   - Obesity
   - Physical inactivity
   - Diet

Natural history of type 2 diabetes

Stage 1: ***Insulin resistance:*** *increased glucose and Non Esterified Fatty Acids (NEFA***)**

Stage 2: ***Increased insulin secretion*****:** *compensatory hyperinsulinemia*

Stage 3: *Impaired glucose tolerance*

Stage 4: ***Overt type 2 diabetes***

Clinical features:

Features of increased osmolality

- Polyuria: increased volume and frequency of urination due to osmotic diuresis induced by hyperglycemia.
- Polydepsia- increased feeling of thirst and drinking excess water/fluid due increased blood osmolality
- Blurring of vision: swelling of the lens due to increased osmolality.

Features of calorie loss

- Polyphagia: feeling of hunger , a need to eat several times a day
- Generalized weakness-
- Weight loss

Some patients may be Asymptomatic mainly Type 2 patients and GDM

Diagnosis is made incidentally during routine medical checkup, ANC follow up etc.

Therefore it is advisable to screen patient for DM, if following risk factors are present:

- *Obesity (BMI >25 kg/m^2),*
- *First-degree relative with DM*

- *History of gestational DM or delivered a baby weighing more than >4kg (9 lb)*
- *Hypertensive,*
- *Hyperlipidemia HDL <35 mg/dl or triglyceride level >250 mg/dl,*
- *History of impaired fasting glucose or impaired glucose tolerance glucose on prior testing.*

Table VII-2-1 Criteria for the Diagnosis of Diabetes Mellitus:

- ***Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL) OR***
- ***Fasting plasma glucose of >126 mg/dl (7 mmol/L) OR***
- ***2-hour postprandial plasma glucose >200 mg/dl after a glucose load of 75 g (during oral glucose tolerance test)***

N.B. These criteria should be confirmed by repeat tests on a different day.

- ***Random*** is defined as without regard to time since the last meal
- ***Fasting*** is defined as no caloric intake for the last 8 hrs.
- ***Oral glucose tolerance test***: blood glucose is measured after ingestion of 75g anhydrous of glucose dissolved in water.
- The patient is said to have impaired glucose tolerance **(IGT**) if the fasting plasma glucose is >110 mg/dl and <126 mg/dl.

Source: Modified from American Diabetes Association, 2004.

Somogyi phenomenon: refers to hyperglycemia secondary to a period of drug-induced hypoglycaemia with metabolic compensation (increased gluconeogenesis and sympathetic outflow). If controlling high glucose becomes a problem (especially a.m. glucose), consider checking for hypoglycemia in the time leading up to high readings.

Treatment:

Goal of therapy. Eliminate symptoms and prevent the complications of diabetes.

- In resource limited setup preventing acute complications that result acute dehydration, coma and premature death.
- Prevention or delaying the occurrence of chronic complications: with tight blood glucose control to to achieve a near normal blood sugar level significantly diminishes risk of developing chronic complications
- In children one should also aspire to achieve normal growth and development.

Biochemical Goals

- *FBS <130 or RBS<200 (Acceptable blood glucose control.)*
- FBS<100 or RBS<160 (ideal but usually difficult to achieve by current technology)

A. Non pharmacologic Therapy

1) **Diet therapy**. Patients should be given proper advice about their diet.
   - Maintenance of a normal Body Mass Index should be the prime target through recommending calories intake according to age, sex and physical activity.
   - Alcohol ingestion should be limited
   - Diet should include 60% to 65% carbohydrates, 25% to 35% fat, and 10% to 20% protein.
   - Patients are advised to significantly decrease cholesterol intake.
   - Avoid simple sugars (e.g. sugar, soft drinks, honey, and other sweets)
   - High fiber diet such as vegetables slow the absorption of digested food in the form of simple sugars
   - Fresh fruit such as water melon and lemon can be freely taken as opposed to oranges bananas that must be taken with caution.
   - Dividing meal into four to six equal parts may helps in achieving stability in some cases
2) ***Exercise***: has multiple positive benefits to diabetic patients including :
   - Cardiovascular risk reduction

- Reduce blood pressure
- Maintain muscle mass
- Reduction in body fat and helps in losing weight.
- It is beneficial to both Type 1 and Type 2 patients

- Therefore regular exercise 20-30 minutes, aerobic exercise such as jogging, walking, swimming etc 3 – 4 days is recommended.
- N.B Patients on Insulin treatment should be cautious to avoid hypoglycemia

3) Weight reduction

- Maintain normal BMI of 20 and 25, Weight loss increase sensitivity to insulin and may lead to decrease in the demand of exogenous insulin or the dose of Oral hypoglycemic agents.

4) Patient education. Involving patients in the their own treatment plan essential.The patient can be involved in his care through regular health education to achieve the ideal knowledge, attitude which is ccrucial to proper management of DM.

Areas of Patient Education

- Patients should be made to understand DM is needs lifelong treatment and follow up
- Goal of treatment should be set together with the patient
- To avoid excess alcohol intake and, smoking
- Benefit of weight reduction, diet and regular exercise
- Proper foot care
- Hypoglycemia causes , symptoms and simple first aid management
- Complications of diabetes
- Insulin injection technique
- Self glucose monitoring

B. Pharmacologic therapy.

1. Insulin

- Beef, pork, and recombinant human insulin (Humulin) are available. Humulin is generally preferable and tends to be less immunogenic than beef or pork insulin and therefore there is less insulin resistance secondary to anti-insulin antibodies.
- Type 1 DM patients must be started on insulin at the time of diagnosis.

- The average daily insulin requirement is approximately 0.3U/Kg/day (25 units /day) in a person with type 1 diabetes in whom the production of endogenous insulin is assumed to be nil.

Table V-2-2 Different preparations of insulin based on their duration of action:

Preparation	***Onset of action***	***Peak action and Duration of action***	***Clinical sue and rout of administration***
Short acting (crystalline /regular)	30-60 min	P : 1-4 hrs D: 4-6 hrs	Used in ketoacidosis for rapid control of high sugar and acidosis. It can be administered IV , IM or SC
Intermediate-acting insulin (NPH or Lente)	1 to 3 hours	P: 6- 12 hrs D:18-26 hrs	Used for ambulatory long term control of sugar level Given not more than twice a day Rout of administration is limited to SC
Long-acting insulin (Ultralente PZI): Long acting (NPH, isophane)	Onset 4 to 8	P:14- 24 hrs D: 28- 36 hrs	Not available for use in our country

Side effects:

- The most serious complication of insulin is hypoglycemia.
- Hypersensitivity, atrophy or hypertrophy of injection sites may also occur, sometimes.

In type 1 DM

For patients diagnosed with DM presenting with Ketoacidosis

- Glucose control is initially obtained with a sliding scale using regular insulin. Measure serum glucose every 6 hours and give sub cutanous regular insulin depending on RBS measurement.

- Once the glucose is stabilized with regular insulin 6 hourly injections, 2/3 of the last 24 hrs insulin requirement is given, in the form of intermediate acting insulin, as S.C injection per day.
- If the total daily requirement of insulin is greater than 40 units , 2/3 of the total insulin requirement given as an AM dose (in the morning) and 1/3 third is given as a PM dose(evening).
- If the intermediate-acting agent does not give adequate control of daytime blood glucose, a short-acting agent may be added.

The other option for patient diagnosed before developing acute complications

- Start with 20- 25 units of Humulin insulin (equivalent to daily insulin production by islets) S.C, daily
- Gradually increase the dose by 3- 5 units very 4- 5 days till acceptable level of blood glucose is achieved

Intensive insulin therapy: to achieve near normal blood glucose level

- ***An insulin pump***, which administers continuous SQ insulin infusion with mealtime boluses, or
- ***Multiple daily insulin injections*** with frequent blood glucose determinations.
- Another option is the use of a long-acting insulin (such as Ultralente) to provide a base of insulin delivery augmented by regular insulin at mealtimes.
- This type of treatment approach needs a lot of commitment from the patient and the physician. It helps to achieve near normal blood glucose level and thus delays the development of chronic complications. It may be complicated by frequent bouts of hypoglycaemia.

2. *Oral hypoglycemic agents*

These groups of drugs are widely used in type 2 patients whose hyperglycemia has failed to be controlled with conservative measures.

a) Sulfonylureas: stimulate pancreatic beta cells to secrete insulin.

Dose: ***Glyburide*** 2.5 to 20 mg PO or

Glipizide 5 to 20 mg PO

- Glyburide is more likely to result in glycemic control when used once a day than is glipizide. Glyburide should be used in a twice-daily dosing if 20 mg/day total is required.

- The effectiveness of sulfonylureas declines up to 10% annually as the failure of beta-cell function progresses.

b) ***Metformin****:* reduces blood glucose levels by improving hepatic and peripheral tissue sensitivity to insulin without affecting the secretion of insulin.

- Metformin is used as monotherapy or in combination with sulfonylureas or insulin for type 2 DM.
- It is especially useful in overweight patients because it does not cause weight gain.
- Hypoglycaemia is not a problem with metformin.
- Metformin also appears to improve plasma lipid and fibrinolytic profiles associated with type 2 DM.
    - **Dose**: Initial dosage is 500 mg PO daily until initial nausea and anorexia are tolerated and then increased to 500 mg BID.
    - The dosage can be increased by 500 mg weekly to maximum dose of 2500 mg if reasonable glycemic control couldn't be achieved.
    - Use with or after food may lessen the GI side effects.
- ***Side effects***: Lactic acidosis (rare). Risk is minimized if metformin is avoided in patients with renal disease, CHF or pulmonary disease.

c) Alpha-glycosidase inhibitors:

- ***Acarbose and Miglitol***: are oral agents that reduce the absorption of carbohydrates, thus reduce postprandial hyperglycaemia.
- Alpha-glycosidase inhibitors can be used as monotherapy or in combination with insulin or sulfonylureas.
- Start with Acrarbose 25 mg with evening meal , may be increased to a maximum dose of 50-100 in weeks
- In general, this group of drugs is less effective than other classes

d) ***Thazolidinediones*** : reduce insulin resistance and increase peripheral glucose utilization

Pioglitazone: 15- 45mg /day in a single daily dose

Rosiglitazone: 2- 8 mg total daily dose given once or in two divided doses

These new group of drugs decrease insulin and sulfonylurea requirement

Side effects: idiosyncratic hepatocelluar injury

The use of Insulin in type 2 DM,

- Insulin is usually added to an oral agent when glycemic control is suboptimal at maximal doses of oral medications.
- An intermediate-acting agent is used starting with a low dose and increasing as needed for glycemic control (such as 5 to 10 U of NPH increasing as needed).
- Adding NPH at bedtime is generally more efficacious than using it during the day.
- If using only insulin, start with an AM (morning) injection. The dose can be increased by 5 U every 3 to 7 days until adequate control is achieved.
- If early morning hyperglycemia is a problem, intermediate-acting insulin can be given twice daily as a split dose.

Follow up of patients:-Since this is a lifelong disease regular follow up of patient is crucial. Points to give emphasis during follow up

- Symptoms of hyper or hypoglycemia
- Wight
- Blood pressure
- Visual acuity
- Examine the oral cavity
- Examination of the feet
- Examine Injection site
- Laboratory tests: blood or urine sugar and urine albumin or protein.

Acute complications of Diabetes Mellitus

1. **Hypoglycemia**
2. **Diabetic Ketoacidosis**
3. **Hyperosmolar Comma**

1) ***Hypoglycemia*** in the diabetic patient is caused by
   - Overdose of insulin or hypoglycemic agents
   - Missing of meal
   - Strenuous exercise

Clinical manifestations

Early: one may feel the effects of sympathetic stimulation such as cold sweat, tremor, hunger or palpitations.

Late: If early symptoms are neglected then symptoms of the effect of hypoglycemia on the brain (Neurogenic manifestations) such as dizziness, blurring, headache, nightmares, and coma may occur.

Management

- Any patient with diabetes losing consciousness should always be considered hypoglycemic until proven otherwise by blood sugar determination and should be managed by rapid IV administration of glucose or PO/ NG tube administration of any concentrated sugar solution.
- Prolonged unconsciousness requires continuous 10% IV glucose administration.

2) Diabetic Ketoacidosis

Definition: is an acute metabolic crisis in patients with diabetes mellitus characterized by:

- Hyperglycemia (blood glucose level may range from 250-600 mg /dl)
- Metabolic acidosis (ketosis)
- Hypotension and features of dehydration

DKA was formerly considered as a hall mark of type 1 DM. However, currently it is known that some type 2 DM patients who are being treated by oral hypoglycemic agent may also develop DKA.

Precipitating factors:

DKA may occur after sever days of worsening diabetic control, or may appear suddenly within few hours.

Some of the precipitating factors are:

- *Intercurrent infection*
- *Poor compliance with insulin or discontinuation of insulin*
- *Dehydration*
- *Stressful conditions such as, trauma, surgery or of emotional crisis*
- *Excessive alcohol ingestion*

Pathogenesis:

Any event that decrease insulin availability or cause stress that increase the insulin demand, lead to sever insulin deficiency and the effect of counter regulatory hormones such as glucagon, cortisol, epinephrine and growth hormone becomes overwhelming. This biochemical changes bring about:

- Increased production of glucose by the liver and increased glycogen degradation to glucose
- Decreased glucose uptake and utilization by muscles
- Lipolysis: enhanced break down of free fatty acids and subsequent ketogenesis. This increases blood levels of keton bodies such as acetoacetic acid, β-hydroxybutyric acid, and acetone, resulting in metabolic acidosis.
- The above biochemical processes result significant hyperglycaemia and Ketoacidosis, which are responsible for the clinical manifestations of DKA.

***Signs and symptoms*:**

- Volume depletion : dehydration- dry tongue and bucal mucosa , poor skin turgor and hypotension
- Kussmaul respiration : deep and fast breathing resulting from metabolic acidosis
- Acetone ("fruity") odour of breath: due too acetone
- Nausea and vomiting and frequent complaint of abdominal pain.
- Mental status changes : lethargy and confusion which may evolve into coma with sever DKA
- Cerebral edema: an extremely serious complication of DKA is seen most frequently in children.
- Signs of infection , which may be precipitating DKA , should be looked for
- A history of diabetes (unless first presentation).

Laboratory Diagnosis:

1. **RBS:** *hyperglycaemia* can be diagnosed with RBS determination. Blood glucose level is usually high (averaging 500 mg /dl)
2. ***Urine dipstick for ketones***: *ketosis* can be determined with bedside reagents. This test is 97% sensitive. Serum keton level can also be measured to confirm hypereketonemia.
3. ***Arterial blood gas analysis*** : can diagnose metabolic acidosis which is indicated by low serum bicarbonate level (usually below 10 mEq / L) and low blood PH (< 7.35)
4. **Additional laboratory evaluation**

a) Electrolytes:

- ***Serum K^+ level:*** look for hyperkalemia or hypokalemia
- ***Serum Na^+:*** tends to be low because of dilution as the osmotic effect of hypergycemia increases ECF volume.
- ***Serum osmolality is high***

b) BUN, creatinine,

c) CXR, urine culture and sensitivity, blood cultures should also be done to identify an infectious process.

Treatment of DKA:

Acute management

1. ***Supportive therapy*:**
   - Airway maintenance, supplemental oxygen as needed, and treatment of shock.
2. ***Fluid replacement*:**

   Fluid replacement corrects dehydration caused by glucose induced osmotic diuresis. The fluid deficit in patients with DKA averages 3-5 L, which should be promptly replaced. Hence give 5- 6 L of fluid in the 1st 24 hours.

   - o Initially 1 L of normal saline (0.9 % NaCl) is given over ½ an hour.
   - o Continue with 1 L of normal saline/hr for the first 2-3 hours
   - o Then ½ normal saline (0.45 % NaCl) at slower rate till the patient is well hydrated.
   - o This will rehydrate the patient and ensure adequate renal perfusion.
   - o When the serum glucose level falls to 200-300 mg/dl, change the IV fluid to 5 % - 10 % DW to prevent hypoglycaemia.
   - o Carefully monitor the urine out put
3. **Insulin:**

   Insulin is administered to increase glucose use in the tissues, to inhibit ketogenesis, and to counter balance the effect of counter regulatory hormones.

   Dosage and administration:

   - 20 Units of regular insulin, 10 U IV and 10 U IM is given with the initial fluid resuscitation. Then 5-10 /hr units or regular insulin is given per hour till the blood glucose level drops to 250-300mg/dl

- Blood glucose determination is done every hour. The expected rate of fall in serum glucose is 75-100 mg/dl/hr.
- When blood glucose reaches a range of 250 to 300 mg/dl, 5 -10 % glucose solution should be infused to prevent hypoglycaemia.
- Insulin infusion should not be stopped until the Ketonemia clears. It is preferable to give 5% or 10% DW with insulin injection, rather than stop the insulin, because insulin is still required to clear the acidosis and ketotic state.
- Shift to sliding scale when keton clears, until precipitating cause is well controlled.
- Shift to intermediate insulin when patient's blood sugar and precipitating factor is under complete control.

4. **Potassium replacement**:

- Serum K^+ level may be increased initially because of K^+ ion movement from ICF to ECF in metabolic acidosis. Later, the serum K^+ becomes low because of both renal loss of K^+ and the movement of K^+ ions back to ICF as the acidosis is corrected.
- Patients with DKA are expected to have a potassium deficit of 300-400 mEq, which should promptly be replaced.
- Start replacing potassium as soon as the patient has adequate urine output.
- Potassium chloride (KCl) is infused at a rate of 20 -40 mEq/hr.
- Monitor serum K^+ level closely.
- Oral potassium can be given if IV potassium is not available. Encourage patients to eat potassium rich fruits such us banana.

5. **Close follow-up of patients**

- **Monitor serum glucose and potassium** as well as urine output hourly.
- **Maintenance fluids** should consist of 0.45% (½ strength) saline with additives as indicated; 150 to 200 ml/hr adjusted according to urine output.
- **Evaluate for potential precipitating factors,** including infection, pregnancy, Myocardial infarction, inappropriate use of insulin.
- **Diet.** Oral intake may resume when mental status of the patient improves and nausea and vomiting are controlled. Initial diet should consist of fluids, and solid diet is may not be resumed until ketoacidosis is corrected.

3) *Hyperglycemic Hyperosmolar State (Non-Ketotic Hyperosmolar Coma*)

- Usually occurs in elderly type 2 DM patients that do not develop ketosis.

- It is often precipitated by serious intercurrent illnesses such as myocardial infarction, stroke, pneumonia, sepsis etc.

Symptoms:

- Such patients present with several weeks history of polyuria, weight loss, and diminished oral fluid intake that is followed by mental confusion, lethargy or comma.

Physical examination:

- Patients have extreme dehydration, hypotension, tachycardia and altered state of consciousness or comma. The dehydration is caused by a hyperglycemia induced osmotic diuresis, when it is not matched by adequate fluid intake.

Laboratory: Very high serum blood glucose level (may range from 600- 1200mg/dl)

Treatment involves

- Fluid replacement : administration of IV fluids and
- Bringing down the blood sugar rapidly by using rapidly acting insulin preparations
- Identifying and treating the precipitating factor

Chronic Complications of Diabetes Mellitus

- The chronic complications of DM affect many organ systems and are responsible for majority of morbidity and mortality associated with the diseases.
- Prevention of chronic complication is one of the major goals of care of the diabetic patients. This is attempted by achieving as near normal blood glucose level as possible.
- Several studies have shown that with tight blood glucose control, the occurrence of chronic complications can be delayed by several years.

1. Retinopathy :

- Is one of the commonest chronic complications and one of the leading causes of blindness in developed countries.
- Symptoms may include difficulty of reading , blurring of vision, shadowing which may later on progress to total blindness,

Classification of Diabetic retinopathy

a) ***Background retinopathy*****:** early changes which is often asymptomatic

- **Microaneurysm:** occlusion of capillaries gives rise to distention and eventual rupture of vessels

- **Dot hemorrhages:**-increased permeability of capillaries and from ruptured aneurysms
- **Hard exudates:** proteins and lipids leak due to increased permeability of capillaries

b) ***Maculopathy***: which manifests with impairment of central vision loss

c) Proliferative retinopathy: asymptomatic unless complicated by hemorrhage

- Characterized by new vessels formation which is stimulated by ischemia

d) Advanced diabetic disease: may cause severe vision loss to the extent of complete blindness

- ***Extensive fibrovascular proliferation*** develops following ischemia and necrosis.
- ***Retinal detachment*** results from the deformity created by extensive fibrosis
- ***Vitreous hemorrhage*** refers to blood in the vitreous hemorrhage.

Management

- Laser therapy
- ASA 100 mg /day may prevents further occlusion of small capillaries
- Surgery : Viterotomy removes blood clots and fibrosis that obstruct vision

2. Neuropathy

Symptoms: include

- Burning sensation, numbness
- Constipation or nocturnal diarrhea
- Impotence
- Foot ulcer

Classification of Diabetic Neuropathy

a) Polyneuropathy:

- Is the commonest neuropathy, characterized by distal symmetrical, predominantly sensory impairment which manifests with tingling sensation, numbness, burning sensation etc.
- It is often progressive and may lead to total loss of sensation and absence of deep tendon reflexes.

b) Radiculopathy: characterized by neurogenic pain. It is often self limiting

c) Amyotropy: atrophy of proximal muscles mainly around the hip girdle

d) **Autonomic Neuropathy:** may manifest with**:-**
   - Postural hypotension
   - GI manifestations: gustatory sweating, gastroparesis, nocturnal diarrhea
   - Genitourinary manifestations: neuropathic bladder, erectile dysfunction (impotence)

e) **Mononeuropathy:** paralysis of a specific nerve or nerves
   E.g. diplopia due to of third and sixth nerves palsies

Neuropathy management

- Symptomatic treatment : pain control
- Diarrhea control
- Treatment of impotence

3. Nephropathy: is a common complication in DM.

Clincal fetures

- Periorbital edema (eye or facial puffiness),pedal edema , anasarca
- Anemia, Uremia and osteodystrophy in patients with end stage renal diseases

Laboratory: Progression from micro albuminuria → Macroalbuminuria

Management

- Tight blood pressure control
- ACE- inhibitors: decreases progression of renal diseases
- Renal transplantation or Dialysis in End stage renal diseases

4. Diabetic Foot Ulcer

The following are underlying mechanism for diabetic foot ulcers

- ***Neuropathy***
  - Loss of pain sensation exposes to injury
  - Loss of sweating results dry skin that is susceptible to injury
- ***Vascular:*** poor blood supply to the foot causes decreased healing of wound poor recovery from secondary infections.
- ***Abnormal Pressure loading***: due to neuropathy (Charcot's joints) or anatomical deformity of the feet. Since the foot is not in a normal anatomic position it is exposed to abnormal load and pressure sores develop.

Symptoms and signs of foot ulcer: numbness and burning, aching pain, swelling, darkening, abscess and cold extremity

Foot care: should be essential part of diabetes care

- *Put on comfortable shoe*
- *Check for pebbles in shoe*
- *Examine the foot daily to detect problems earlier*
- *Wash dry and oil the feet*
- *Take caution during nail cutting*
- *Treat athletes' foot or any other foot infection as early as possible*
- *Remove corn*
- *Do not use hot water to wash the feet*
- *Stop smoking*

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3. Thyroid disorder

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define different forms of thyroid disorders.*
2. *Describe the pathophysiology of diseases of the thyroid.*
3. *Understand the epidemiologic significance of diseases of the thyroid.*
4. *Identify the clinical manifestation of diseases of the thyroid, with special emphasis on hyperthyroidism and hypothyroidism.*
5. *Understand the diagnostic approach of diseases of the thyroid.*
6. *Manage patients with common thyroid diseases.*
7. *Understand the prevention of some preventable thyroid diseases.*

Introduction:

- The thyroid gland normally weighs 20gm and is visible in thin women. The basic unit of thyroid structure is a follicle which is spherical in shape, filled with colloid, and encompassed by single epithelial cell layer. The colloid consists of thyroglobulins in which thyroid hormones are stored. About 40 follicles form a lobule, a group of lobules form a gland. The hormones produced by the thyroid gland are referred to as tri-iodothyronine (T_3) and thyroxin (T_4).

Thyroid disorders:

- Manifest with qualitative or quantitative alteration of thyroid hormone secretion, enlargement of thyroid, or both.
- Decreased production of these hormones leads to what is referred to as hypothyroidism, which results in a state of declined metabolic activity.
- Increased production on the other hand leads to hyperthyroidism, which in turn results in a state of increased metabolic activity.
- Goiter is a diffuse or focal enlargement of the thyroid gland that may be metabolically hyperactive, hypoactive, or normoactive (Euthyroid)

Transport and Metabolism of hormones

- Of the total hormone in the blood, 80% is found in the form of T4 and 20% in the form of T3.

- Ninety nine percent of hormones is bound to carrier proteins (thyroglobulin) and is not physiologically active, and it is only the remaining 1%, which is found free in the serum, which is physiologically active.

The advantages of carrier proteins are:

- They are reservoirs to replenish free hormone level
- They buffer any fluctuation in gland secretion
- They protect against hepatic degradation and renal excretion of the hormone

Standard lab tests measure protein bound hormone level so that results depend on the concentration of these proteins. Therefore the hormone level alterations could be apparent like when the thyroglobulin (TGB) level shifts or real when the TBG remains constant but hormone level varies.

- ***Conditions in which TBG is increased are*** : pregnancy, contraceptive (estrogen) , androgen , infectious hepatitis
- ***Conditions in which TBG is decreased are*** : steroid, chronic liver diseases

Metabolic actions of thyroid hormones:

Acting through nuclear receptors, these hormones play a critical role in are to regulate

- Cellular differentiation during development
- Maintain thermogenic and metabolic homeostasis in adults

Regulation of hormone production:

- Hypothalamic TRH stimulates pituitary production of TSH, which in turn stimulates thyroid hormone synthesis and secretion.
- The presence of adequate thyroid hormone sends a negative feedback signal that inhibits TRH and TSH production.
- When the level of thyroid hormone in the serum decreases the production and release of TRH and TSH is enhanced.

TSH, secreted by thyrotrope cells of the anterior pituitary, plays a pivotal role in control of pituitary - thyroid axis and serves as the most useful physiologic marker of thyroid hormone function.

Thyroid function tests:

1. **Serum T_3 and T_4 level**: measures the total bound (99 %) and free (1 %) hormone level in the circulation. This gives some clue about serum level of thyroid hormone, but has limitation since serum level of the hormone is influenced by conditions affecting the level of carrier proteins.

   T3 and T4 levels are elevated in hyperthyroidism and decreased in hypothyroidism.

2. **Serum TSH level:** is the most important test to asses thyroid hormone function.
   - ***In hypothyroidism***, TSH level is elevated, as a result of feedback effects of low thyroid hormone level. It is a very sensitive test and, because it usually becomes elevated even before thyroid hormone (T3 and T_4) level decline below normal.
   - ***In hyperthyroidism***, TSH level is decreased, because the elevated thyroid hormone concentration, leads to suppression of TSH release, through a negative feedback mechanism. It is a very sensitive test, because TSH may be suppressed even when thyroid hormone level are not elevated above normal range.
3. **Radioactive iodine uptake (RAIU):** by the thyroid gland 24 hrs after administration of the Iodine (***I_{131}***) isotope, assesses the rate of iodine uptake by the thyroid gland which demonstrates the degree of glandular activity.
   - Increased uptake in hyperthyroidism, and decreased uptake in hypothyroidism.
   - This test is especially useful in diagnosing ectopic hormone production
4. **Thyroid stimulating antibodies**, **circulating antibody against T_3 and T_4** is an evidence for autoimmune disease of thyroid glands.

Common disorders of Thyroid gland

A. ***Sick euthyroid syndrome (SES)***
B. ***Simple nontoxic goitre (SNG)***
C. ***Hypothyroidism***
D. ***Hyperthyroidism***
   i. ***Graves***
   ii. ***Toxic multinodular goiter(TMNG)***
   iii. ***Toxic solitary nodular (TSN)***
   iv. ***Jodbasdow phenomena***

E. Thyroiditis

F. Thyroid carcinoma

Epidemiology of Thyroid Diseases is Ethiopia

- Simple nodular goiter is very common in areas where there is serious iodine deficiency.
- Among 373 patients seen at the Endocrinology unit of Tikur Anbessa teaching hospital, between 1986 to 1991, 68% of all cases came for a thyroid disorder. Of these 44% were thyrotoxic, 24% has solitary nodules, 29% simple toxic goiter, while thyroiditis and hypothyroidism were rare.
- Among the thyrotoxics 42% were due to Graves' diseases, 32% due to Toxic multinodular goiter, and 22% due to toxic nodule.

A. Sick Euthyriod Syndrome (SES)

- This is a state in which serum level of thyroid hormones is abnormally low or high but patients are not symptomatic.
- Such clinical condition often results from severe illness, physical trauma, stress during which the thyroid hormone level may be low.
- In elderly patients taking drugs containing Iodine, serum level of thyroid hormones may be abnormally high. Patients however remain asymptomatic probably due to decreased impact on peripheral tissue.

B. Hyperthyroidism

Definition: Hyperthyroidism is a hypermetabloic state, resulting from excessive thyroid hormone function.

Thyrotoxicosis is defined as the sate of thyroid hormone excess.

Etiology:

Common causes of hyperthyroidism include:

- Graves'diseases
- Toxic multinodular goiter
- Toxic adenomas

Graves' disease:

- Is the most common cause of hyperthyroidism in the third and fourth decades. It is common in women.
- This is an autoimmune diseases caused by abnormal thyroid stimulating immunoglobulin of IgG class which has long acting thyroid gland stimulating effect.
- It causes a diffuse, symmetrically enlarged thyroid gland, with normal to slightly soft consistency.
- It is associated with ophthalmopathy, dermatopathy and pretibial myxedema.
- There is hyperthyroid state.

Toxic multinodular goiter:

- It usually develops insidiously in a patient who has had a nontoxic nodular goiter for years.
- The thyroid gland is irregular, asymmetric and nodular in nature.
- This clinical condition may occur when a nontoxic multinodular goiter has been exposed to excess iodine intake or when one of the nodules become autonomous (fails to fall under control of TSH-T_3 ,T_4) feedback axis

Solitary hyperfunctioning adenomas:

- The thyroid gland contains a smooth, well-defined, soft to firm nodule that shows intense radioactive uptake on scan with absence of uptake in the rest of the gland.
- Most patients with solitary adenomas do not become thyrotoxic. When they do, they are usually less toxic than those with Graves' disease, and they do not develop ophthalmopathy or pretibial myxedema.

Autoimmune thyroiditis/ Hashimoto's thyroiditis:

- Normal-sized or enlarged nontender thyroid gland.
- Thyroid antibodies, when present, are high in titer.
- This disorder improves spontaneously but frequently recurs.

Excess exogenous thyroid hormone administration:

- May occur because of dosage errors or occasionally in individuals taking large doses of thyroid hormones to lose weight or increase their energy.
- The thyroid gland is normal or small in size.

Subacute thyroidits and viral thyroiditis:

- Tender, diffusely enlarged thyroid gland with a normal or elevated T4 and an elevated ESR.
- Probably of viral origin and may manifest as a sore throat.

Rare causes: Radiation thyroiditis, thyroid carcinoma, excessive TSH stimulation, excessive iodine intake, struma ovarii, and trophoblastic disease.

Clinical features:

- ***Metabolic changes:*** elevated basal metabolic rate, weight loss with increased appetite heat intolerance and sweating
- ***Cardiovascular effects:***
  - Weakness, dyspnea on exertion
  - Palpitation , sinus tachycardia , atrial fibrillation in the elderly
  - Systolic hypertension , high output failure with wide pulse pressure
- ***Gastro Intestinal symptoms:*** loss stool or diarrhea (may be the first sign of thyroid storm)
- ***Skin and hair changes:*** the skin is warm and moist because of peripheral vasodilation , fine silky hair is characteristic finding
- ***CNS and neuromuscular effects***
  - Nervousness, hyperactivity, irritability, dysphoria, emotional lability, poor concentration
  - Fine Tremor
  - Muscle weakness and fatigue proximal myopathy
- ***Genitourinary manifestations*** :Polyuria, dysmenorrhea, oligomenorrhea or amenorrhea
- ***Ophthalmopathy***
  - ***Wide stare and lid lag*** (i.e. slow closing of the upper lid when the eye moves down ward , revealing sclera between the lid and cornea) may occur in any form of hyperthyroidism
  - ***Exophthalmus:*** true thyroid exophthalmus is seen only in Graves' diseases, occurring in approximately 50 % of cases.
    - The eyes are pushed forward because of mucinous and cellular infiltration of extraocular muscles
    - There is inflammation of the conjunctiva and surrounding tissue

- The patient may complain tearing, eye irritation, pain and double vision. In sever case vision may be threatened.

- ***Other findings***
  - Gioter
  - Gynecomastia

Features specific to Graves' disease

- ***Thyroid gland is diffusely enlarged*** and smooth in consistency , bruit/thrill may be heard over it
- ***Ophthalmopathy***: exophthalmus
- ***Thyroid dermopathy***: pretibial myxedema which is non inflamed indurataed plaque
- ***Thyroid acropathy***: clubbing

Diagnosis:

- TSH is elevated in 98 % of patients. It is the best screening test.
- Serum T3 and T4 level (free or total) may be raised
- Antithyroid antibodies: antimicrosomal antibody and antifollicular cell antibody, antithyroglobulin antibody, thyroid-stimulating antibody; elevated especially in autoimmune thyroiditis.

***Treatment*:**

Graves' disease:

1. **Antithyriod drugs:**

- Inhibit the oxidation of iodine and coupling of iodotyrosines, thus decrease the synthesis of thyroid hormone. PTU in addition decreases the conversion of T4 to T3 in peripheral tissues

  Dose: Propylthiouracil: 100 to 150 mg every 8 hours, **or**

  Methimazole: 15 to 60 mg divided every 12 hours depending on severity of illness.

- Although blockade of hormones synthesis is rapid, clinical improvement occurs after few weeks or months, because a large pool of stored hormone continues to be released from thyroid.
- The patient becomes euthyroid 2 to 3 months after beginning therapy.

- Propylthiouracil may achieve results faster because it prevents the peripheral conversion of T_4 to active T_3.
- After clinical improvement, the dose of the medication is tapered to the lowest dose to maintain euthyroid state and the drug is continued for 1 - 1 ½ yrs.
- A free T_4 level should be checked after 1 month of therapy and then every 2 to 3 months.

Side effects /drug toxicity

- Skin rash or joint pain
- Agranulocytosis

Advantages of Atithyroid drugs:

- Hospitalization , surgery and anesthesia are avoided
- The occurrence of post treatment hypothyroidism is less likely

Disadvantages:

- Permanent remission occurs in fewer than 50 % of patients
- Treatment success depends on patient compliance to treatment

2. **Radioactive iodine**
   - **Iodine ^{131}**, 5 to 15 mCi, a single dose of ^{131} I, causes a decrease in function and size of the thyroid gland in 6- 12 weeks.
   - Approximately 75 % of patients with Graves' disease are made euthyriod by a single dose.
   - Those who are still thyrotoxic after 12 weeks are given a second dose. Additional dose can be given if needed.
   - Eventually, almost all patients are cured in this way.
   - ^{131} I treatment may be preceded and followed by antithyroid drugs.

Advantages:

- Hospitalization , surgery and anesthesia are avoided
- The rate of cure is almost 100%
- Little patient compliance is required

Disadvantages:

- There is a risk of treatment induced hypothyroidism

Pregnancy is an absolute contraindication to ^{131}I therapy.

3. **Inorganic iodine** rapidly controls hyperthyroidism by inhibiting hormone synthesis and release from the gland.

- One drop of saturated potassium iodide solution in juice is taken daily.
- This should not be used as the sole form of therapy.
- It may be used alone for 7 to 10 days before surgery to decrease the vascularity of the thyroid gland.

Surgery: Subtotal thyriodectomy - usually reserved for those who are unable to take antithyroid drugs

Preparation for surgery:

- Operation on thyrotoxic patient produces the risk of thyroid storm; therefore, treatment should be initiated with atntithyriod drugs, long enough in advance for patients to return to a euthyriod state before surgery. Inorganic iodine may be given to decrease vascularisation before surgery.

Advantages of surgery

- Cure of hypothyroidism is rapid
- The success rate is high , most patient are cured
- Patient compliance is required for shorter period

Disadvantages

- The patient must be hospitalized , and surgical and anesthetic risks are incurred
- Surgical complications include : hypothyroidism and recurrent laryngeal nerve paralysis

Other symptomatic treatments:

- **Propranolol:** 80 to 200 mg/day in divided doses every 6 hourly, will reduce symptoms of tachycardia, palpitations, heat intolerance, and nervousness but will not normalize the metabolic rate. It should not be used alone except in the case of transient hyperthyroidism secondary to autoimmune (viral) thyroiditis.

Ophthalmopathy:

- Smoking can worsen ophthalmopathy. Ophthalmopathy may also worsen (usually transiently) with radioactive iodine.
- This can be prevented by treatment with prednisone (0.5 mg/kg PO for 3 months starting 2 to 3 days after radioactive iodine). However, this carries the risk of prednisone exposure.

- o Symptomatic treatment for ophthalmopathy includes artificial tears or methylcellulose drops for the discomfort, patching or prisms for diplopia, diuretics and raising the head of the bed for circumorbital edema.

Treatment of other causes of hyperthyroidism

- **Toxic multinodular goiter** is treated with surgery or I^{-131}.
- **Solitary hyperfunctioning adenomas are treated with I^{-131} or surgery.**
- **Autoimmune thyroiditis** is transient and does not require definitive treatment except in those patients with recurrent hyperthyroidism. Propranolol may be used alone if symptoms are mild. Antithyroid drugs may be needed for a short time in some patients.
- **Subacute thyroiditis** and viral thyroiditis generally self-limited but should be treated with aspirin 650 mg QID. In more severe cases, prednisone may be used at 40 mg PO QD, tapering to 10 mg each day over 2 weeks, and then continued for 1 month after patient becomes asymptomatic. Resolution of symptoms usually occurs in 1 to 6 months, and relapse is common. Hypothyroidism may occur but is rare.

Thyroid storm

Definition: A severe life-threatening form of hyperthyroidism.

Etiology: Increasing stress such as trauma or illness may cause this in a previously mildly hyperthyroid patient.

Signs and symptoms: Have signs and symptoms consistent with thyrotoxicosis (tachycardia, heat intolerance, weight loss), as well as fever, confusion, agitation, weakness, dyspnea, diarrhea, and shock.

Treatment:

When suspected, treatment should be instituted immediately.

Supportive therapy:

- ***Control fever:*** Fever is controlled with acetaminophen and a cooling blanket. If fever is not controlled within several hours, concurrent infection should be suspected. Other signs of hyperthyroidism may require several days of therapy before improvement is seen.
- **Propranolol** 20 to 40 mg QID to control tachycardia, tremor,
- ***Fluid and electrolytes*** : should be replaced

Antithyriod treatment

- ***Propylthiouracil:*** 250 mg PO QID (Or ***methimazole*** 20 to 40 mg PO or per NG Q6-8h).
- Alternative is 0.5 g of sodium iodide in 1 L of NS over 12 hours.
- **Give steroids** equivalent to about 300 mg of hydrocortisone per day (100 mg IV TID Q8h). Dexamethasone has some theoretical advantage because it prevents conversion of T_4 to T_3 peripherally.
- **Avoid aspirin** because it may increase circulating active T_3 and T_4 by reducing protein binding.

C. Hypothyroidism

Definition:

Primary hypothyroidism: refers to a thyroid hormone deficiency as a result of thyroid gland disease. *Secondary hypothyroidism*: results from TSH deficiency.

Tertiary hypothyroidism: results from thyrotropin-releasing hormone (TRH) deficiency.

Etiology:

Without thyroid enlargement

- Hypothyroidism frequently develops following treatment of Graves' disease with 131I therapy or thyriodectomy.
- Idiopathic hypothyroidism: is idiopathic atrophy of the thyroid gland. It is one of the commonest causes of hypothyroidism.
- Developmental defects and TSH or TRH deficiency are less common causes.

With thyroid enlargement

- ***Chronic thyroiditis /Hashimoto's thyroiditis*** is one of the most common causes of spontaneous hypothyroidism.
- Drugs, iodine deficiency, and inherited defects in thyroid hormone synthesis are rare causes.

Signs and symptoms:

- Fatigue, weakness, lethargy, slow movement, cold intolerance
- Slight to moderate weight gain , but appetite tends to be diminished
- Carpal tunnel syndrome, edema of the face and extremities,
- Hearing loss, hoarseness of the voice
- Dry skin , hair loss , sparse eyebrows with loss of the lateral half

- Pericardial effusion and ascites occasionally occur
- Constipation
- Menorrhagia,
- Memory impairment
- Psychosis may develop with long-standing hypothyroidism and may be precipitated by thyroid hormone replacement

Physical examination

- Thickened, puffy features is due to accumulation of mucinous mucoplysaccharide-rich material in tissues .This is known and myxedema
- Yellowish dry skin
- Nonpitting edema
- Hypothermia
- Bradycardia
- A delay in return phase of Achilles and other deep tendon reflexes is a specific finding.
- Loss of the lateral portion of the eyebrows (madarosis)

Effect of hypothyroidism on organ systems

- ***Cardiovascular system :*** Decrease in cardiac output ,Pericardial effusion
- ***Respiratory system :*** Hypoventilation ,Plural effusion
- ***Gastrointestinal tract :*** Constipation
- ***Nervous system:*** Decreased mental function , Psychiatric changes (e.g. psychosis , depression)
- ***Blood:*** Normocytic normochromic anemia.

Cretinism: is sever hypothyroidism beginning in infancy infants may have

- Hypotonia, umbilical hernia,
- Delayed mental and physical development, and mental retardation may result if hypothyroidism goes untreated in the first few years of life.
- Shot limbs and a large head , with a bread flat nose , widely set eyes , and a large tongue characterize this form of dwarfism
- Other signs and symptoms typical of adult patients may also be seen

Diagnostic workup:

Thyroid function tests:

1. ***Serum TSH level:***

- Increased serum concentration of TSH is the earliest and the most sensitive indicator of primary hypothyroidism.
- Low TSH value indicates a secondary (pituitary) or tertiary (hypothalamic) hypothyroidism. Both are rare causes of hypothyroidism.
- Serum T_3 and T_4 level are decreased

2. **Other laboratory abnormalities may include** :
   - High AST, low sodium, low blood glucose, elevated CPK,
   - Elevated cholesterol and triglycerides,
   - Mild normocytic normochromic anemia,
   - Elevated prolactin levels secondary to high TRH levels, and
   - ECG: flat or inverted T waves with minor ST-segment depression and low amplitude

Treatment:

Thyroid hormone replacement: L-thyroxin, a synthetic agent is the treatment of choice.

The goal of therapy is to normalize the TSH.

Initiation of treatment:

Slow initiation:

- Patients with severe hypothyroidism, older patients and patients with cardiovascular disease, may have an increased sensitivity to thyroid hormone, and are at risk of acute cardiovascular and other complications, if hypothyroidism is corrected too quickly.
- Therefore, these patients should be given a very small dose of thyroid hormone initially (25 *µg* of L-thyroxin) which is gradually increased (every 2 to 4 weeks) to a full maintenance dose during 6-12 weeks period.

Rapid initiation

- Younger patients and patients with less sever hypothyroidism, may be started on slightly higher dose (50 µg of L-thyroxin) and advanced to a full replacement dose more quickly (e.g. , the dose may be raised to 100 *µg* two weeks and 125 -150 *µg in another 2 weeks)*
- Check the TSH 2 to 3 months after changing the L-thyroxin dose.

Maintenance therapy

- Most patients require 75 -100 *µg* of L-thyroxin daily
- When symptoms of hypothyroidism have resolved, the dosage should be further adjusted so that serum TSH and thyroid hormone level are maintained in the normal range

Cautions

- Elective surgery should be avoided in hypothyroid patients because respiratory depression commonly occurs.
- Increased sensitivity to narcotics and hypnotics is also common in the hypothyroid patient.

Myxedema Coma

Definition: Myxedema coma results from severe chronic hypothyroidism, which is left untreated, and is life threatening clinical condition.

This serious condition may occur gradually (over years) or more acutely in response to a precipitating factor such as exposure to cold, infection, hypoglycemia, respiratory depressants, allergic reactions, or other metabolic stress.

Clinical features:

- Hypothermia, hypoglycemia, shock, hypoventilation, and paralytic ileus
- Severely impaired level of consciousness
- The mortality rate is 50 % -75%

Treatment: must be started rapidly, despite the risk associated with sudden hormone replacement

L-thyroxin (T_4) 500 µg is given as IV bolus injection, followed by oral L- thyroxin 100 *µg* QID.

Ancillary treatment:

- Temporary use of glucocorticosteriods
- Respiratory support
- Hypothermia and heat loss should be avoided

D. Thyroid enlargement

Goiter

- A goiter is a simple enlargement of the thyroid gland.
- It is more common in females with the highest incidence in the second through sixth decades of life.

- Diffusely enlarged goiters are caused by iodine deficiency or excess, congenital defects in thyroid hormone synthesis and drugs (e.g., lithium carbonate) dietary causes such as cabbage, soybean, cassava etc.
- Most are asymptomatic. It is unusual to have pain and rare to have hoarseness and tracheal obstruction.
- Thyroid function tests should be performed on all patients with goiter because it can be associated with hypothyroidism, euthyroidism, or hyperthyroidism.

Multinodular Goiter

Etiology: most often caused by iodine deficiency.

Signs and symptoms:

Symptoms:

- Thyromegaly, occasionally with rapid enlargement and tenderness secondary to haemorrhage into a cyst.
- Rarely, tracheal compression may occur, causing coughing or choking.
- Some patients may complain of a feeling of lump in the throat.

Physical exam

- Many nodules of varying sizes are usually palpable. Occasionally it may be difficult to distinguish from the typically lobulated, irregular Hashimoto's gland.

Diagnosis:

- Thyroid function tests: Performed to rule out hypo or hyperthyroidism
- Malignant transformation is rare, but should be considered if the gland is enlarging rapidly or hoarseness develops.

Treatment:

The main indications for treatment are compression of the trachea or esophagus and venous-outflow obstruction.

For nontoxic multinodular goiter, the treatments include:

- Surgery
- Raradioiodine therapy ,
- L-thyroxin suppression therapy: decreases TSH level and help to decrease the size of the goiter.
    - Such therapy should not be given to patients with angina or other known heart disease unless the patient is hypothyroid.

- If thyroid enlargement persists despite adequate TSH suppression, a needle biopsy or subtotal thyriodectomy should be considered.

For toxic multinodular goiter, options are

- Antithyroid agent
- Surgery
- Radioiodine, and more recently
- Percutaneous injection of ethanol in to the toxic nodule

Solitary Nodules

- They are usually benign.
- One should, suspect malignancy in a patient with a history of radiation exposure, rapid enlargement, hoarseness or obstruction, and a solid nodule that is cold on scan.

Diagnosis:

- History and
- Radio iodine thyroid scan should be done on every patient with a solitary nodule. Hot nodules that take up the radioisotope are generally benign but fine-needle aspiration of a solitary nodule is prudent.

Treatment:

- Is indicated if signs of compression of trachea, esophagus, significant growth, and recurrence of a cystic nodule after aspiration.
- Similar to multinodular goiter: surgery, thyroxin, or radioiodine for nontoxic nodule; Antithyriod agent, Surgery, radioiodine for toxic nodule.

Subacute Thyroiditis/granulomatous thyroiditis

Etiology: the cause is generally considered as viral. Mumps and Coxackievarus have been suspected as causes.

Clinical features:

- ***Early symptoms***: prodromal phase of malaise, upper respiratory symptoms, and fever that lasts 1-2 weeks. Then the Thyroid gland becomes enlarged, firm and tender, with pain radiating to the ears, neck, or arms.
- ***Hyperthyroidism*** may occur, due to thyroid hormone leaking from damaged follicles in to the circulation.

Disease course: the thyroid pain and the hyperthyroidism subside in few weeks to months. The gland usually return to normal size, if enlargement persists, chronic thyroiditis should be suspected.

Diagnosis;

- Acutely swollen, tender an painful thyroid gland associated with symptoms of hyperthyroidism
- ***Radioactive uptake***: low radioactive iodine uptake in the face of high serum T_3 and T_4 level. This is because the follicles are damaged are unable to trap iodine.

Therapy is symptomatic: because the diseases are self limited

- Aspirin , NSAID and Corticosteroids (in severe cases) to relive the pain and tenderness
- β-blockers can be used to relive symptoms of hyperthyroidism .

Chronic Thyroiditis (Hashimoto thyroiditis)

Etiology: it is an autoimmune disorder that mainly affects women. Antithyriod antibodies are present in most patients.

Clinical features

- *Thyroid gland enlargement*: is the main clinical manifestation, is the result of autoimmune damage that leads to lymphocytic infiltration, fibrosis and weakens ability of the thyroid to produce hormone.
- ***Pain and tenderness*** of the gland in subacute thyroiditis
- ***Hypothyroidism*** is present in approximately 20 % of patients

Diagnosis: is suspected in any patient with firm, nontoxic goitre

- ***Serology***: high titer of antithyroglobulin antibodies, antimicrosomal antibodies
- ***Thyroid function tests*** are often normal unless the patient has hypothyroidism

Therapy:

- L-thyroxin often decreases the size of the gioter and it is useful even in patients with normal thyroid function

Malignancies of the thyroid

Epidemiology:

- Thyroid cancer is common; it is found at autopsy in approximately 5 % of patients with no known thyroid diseases

- It is usually an indolent cancer and tends to remain localized to the thyroid for many years , which is the reason for the low morality rate

Etiology:

- ***Genetic factors*** : one form of thyroid cancer , medullary c.a. has familial tendency
- ***Radiation exposure***: the incidence of thyroid cancer is increased among atomic bomb survivors.

Types/ Classification:

- ***Papillary carcinoma*** : which accounts for 60 % of all thyroid cancer
  - Affects younger age group – 50 % of patients are younger than 40 years
  - Papillary Ca metastasize through the lymphatic system
- ***Follicular carcinoma;*** comprises 25 % of all thyroid cancer
  - Histologicaly resembles normal thyroid tissue ,
  - Follicular Ca metastasizes hematogenously
- ***Medullary carcinoma***: which accounts for 5 % of all thyroid cancers. Arises from parafollicular cells.
  - Produce calcitonin, patients may have diarrhea.
  - May be associated with multiple endocrine neoplasia syndromes, **MEN type II**
  - Approximately 20 % of these carcinomas are familial.
- ***Anaplastic carcinoma:*** account for 10 % of thyroid cancer, usually affects patients older than 50 years of age and is highly malignant.
- ***Other rare malignancies*** (lymphoma, sarcoma etc.); secondaries of other tumours

Signs and symptoms:

- A hard nodule in the thyroid is usually the first sign.
- Late signs: hard, immobile thyroid, attached with skin, cervical or supraclavicular lymph nodes enlarged, hoarseness, Horner syndrome, throat/ear/head pain, stridor, dysphagia, venous congestion.

Diagnosis:

- Ultrasound: nodules
- Scintigraphy/radioiodine uptake: cold nodules without or little uptake
- CT/MRI of neck
- FNA with cytology or biopsy
- Serum Calcitonin level ,
- Staging is based on : CXR, CT, bone scintigraphy

Treatment: Always combine

- Surgery: total thyroidectomy and neck dissection
- Radiotherapy: external radiation in Anaplastic carcinoma
- Nuclear medicine: ^{131}I ablative radiotherapy.
- Give T4, as high a dose as possible, to suppress TSH-effect on remaining metastases.

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4. Diseases of the adrenal gland

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define different types of diseases of the adrenal gland.*
2. *Describe the pathophysiology of diseases of the adrenal gland.*
3. *Identify the clinical manifestation of diseases of the adrenal gland, with special emphasis on Cushing's syndrome and Addison's diseases.*
4. *Understand the diagnostic approach of diseases of the adrenal gland.*
5. *Manage patients with common diseases of the adrenal gland.*

Common Adrenal gland diseases

1. ***Disease of the adrenal cortex***

a) ***Resulting from excess production of hormones***

- ***Cushing's syndrome :*** excess cortisol production
- ***Primary hyperaldosteronism*** : excess production of aldosteron

b) ***Inadequate production ;***

- ***Addison's diseases :*** inadequate production of cortisol and aldosteron

2. ***Disease of the adrenal medulla***

- ***Pheochromocytoma***: excess production of catecholamine

Cushing's Syndrome (Hypercortisolism)

Cushing's syndrome*:* is caused by excessive concentration of cortisol or other glucocorticoid hormones in the circulation

Etiology:

a) ***Bilateral adrenal hyperplasia (Cushing's diseases)*** is the commonest cause of Cushing's syndrome. It is caused by increased pituitary secretion of ACTH. Pituitary tumors large enough to be seen by skull x-ray, are present in more than 10 % of these patients, and smaller basophilic adenomas are found in more than 50 % of patients.

b) ***Adrenal adenomas and adrenal carcinoma*** may produce excess cortisol

c) ***Ectopic ACTH production by tumors*** , such as oat cell carcinoma of the lung, carcinoma of the pancreas , bronchial carcinod tumors , and other, cause adrenal hyperplesia and Cushing's syndrome

d) ***Iatrogenic Cushing's syndrome***: is seen more often than spontaneous occurring syndrome. It is an expected complication in patients receiving long term glucocorticiod treatment for asthma, arthritis, and other conditions.

Clinical features

- ***Central obesity*** is caused by the effect of excess cortisol on fat distribution. Fat accumulation in the face, neck and trunk, while thelimns remain thin. The **"moon face**" , "**buffalo hump"** (cervical fat pad) and **supraclavicular fat pads** contribute to the Cushingiod appearance
- ***Hypertension :*** result from the vascular effects of cortisol and sodium retention
- ***Decreased glucose tolerance***: is common, 20 % of patients have overt diabetes. This is a result of hepatic gluconeogenesis, and decreased peripheral glucose utilization.
- ***Symptoms of androgen excess*** (e.g. oligomenorrhea, hirsutism, and acne) may occur in women with Cushing's diseases, because of stimulation by ACTH of adrenal androgen production.
- ***Purple striae***: are linear marks on the abdomen, where the thin, wasted skin is stretched by underlying fat. Atrophic skin with senile purpura may also be seen.
- ***Muscle wasting and weakness:*** reflects the catabolic effect of cortisol on muscle protein.
- ***Osteoporosis:*** is caused by increased bone catabolism.
- ***Susceptibility to bruising:*** is probably caused by enhanced capillary fragility.
- ***Psychiatric disturbance***, especially depression, are frequently seen.
- ***Poor wound healing:*** due to impaired immune function.
- ***Growth retardation*** in children may be severe.

Diagnosis:

1. ***Overnight Dexamethasone suppression test :*** is recommended as an initial screening test

   Administer dexamethasone 1 mg PO at 11 PM at midnight and measure serum cortisol at 8:00 AM the following day

   The serum cortisol level should be <5 *μg*/dl in most individuals, indicating normal suppression of ACTH and cortisol by dexamethasone. Because this test is sensitive, the diagnosis of Cushing's syndrome need not be considered further in these cases.

Patients with Cushing's syndrome will have cortisol level > 5 *μg*/dl usually greater than 10 μg/dl .This result indicates further study is needed.

2. ***The standard dexamethasone suppression test:*** is the most relied up on test for Cushing's syndrome

Table VII-3-1 Standard Dexamethasone Suppression Test in the diagnosis of Cushing's syndrome

	Method	
Day	Dosage of Dexamethasone	Measurement
1	None (baseline)	24 hrs urinary 17-hydroxycorticosteriod and 4 PM serum cortisol level
2,3	Low dose (O.5 mg dexamethasone PO QID)	Repeat measurement on day 3
4,5	High dose dexamethasone 2 mg every QID	Repeat measurement on day 5

Response		
Diagnosis	***Suppression with low dose***	***Suppression with high dose***
Normal	Yes	Yes
Cushing's diseases	No	Yes
Adrenal tumor or ectopic ACTH production	No	No

3. ***ACTH measurement :*** may help to differentiate the cause of Cushing's syndrome
   - ***a.*** *High normal or slightly elevated A****CTH→Cushing's diseases***
   - ***b.*** *Markedly elevated ACTH* ***→ Ectopic ACTH production***
   - c. *Extremely low ACTH level****→ automatically functioning adrenal tumor*** is the source of excess cortisol. Pituitary secretion of ACTH is suppressed due to the excess cortisol

4. ***Serum cortisol level:*** in normal in individuals is highest in early morning and decreases throughout the day, reaching a low point at about midnight. Although the morning level may be increased in patients with Cushing's syndrome, a loss of the normal diurnal variation and an increase in the evening level are more consistent findings.
5. ***The 24 hrs urinary free cortisol excretion rate***: is increased in most patients with Cushing's syndrome
6. ***Other tests:*** lukocytosis , with relatively low percentage of lymphocytes and eosinophils
7. ***Radiologic findings***
    a. ***Skull x-ray:*** enlargement of sella turcica in 10 % of patients with Cushing's syndrome who have macroadenoma.
    b. ***CT scan with injection of contrast medium :*** detect approximately 50 % of pituitary adenomas
    c. ***CT scan of the adrenal gland:*** reveal most adrenal tumors. Uniform enlargement of both adrenal glands suggests an ACTH dependent Cushing's syndrome (ether Cushing's disease o r the ectopic ACTH syndrome ***)***

Therapy

1. ***Adrenal adenoma :*** complete surgical resection of the adenoma cures the disease , but patients may need cortisol replacement post operatively for several month***s***
2. ***Ectopic ACTH syndrome:*** can be cured by treating or removal of the tumor that is producing the ectopic ACTH.
3. ***Cushing's Disease***
    a. ***Pituitary radiation :*** is effective in children but it cures fewer than 1/3 of adult patients
    b. ***Bilateral adrenalectomy*** cures Cushing's diseases***.***

    Disadvantages

    - Patients will develop **Addison's disease** and need lifelong Cortisol replacement
    - **Nelson's syndrome**: in which pituitary adenomas undergo rapid growth, perhaps because it is no longer inhibited by above normal level of cortisol***.***

    c. ***Transphenoidal pituitary surgery:***

    - Is the treatment of choice, even when tumor cannot be seen on CT scan or MRI , transspheniodal exploration may disclose a microadenoma.

- Surgery is successful in 50%-95% of cases and is followed by normal pituitary and adrenal function as well as cure of Cushing's diseases.

A. Hyperaldosteronism

Aldosteronism: is a syndrome associated with hypersecretion of the mineralocorticoid, aldosterone.

Etiology:

1. ***Primary aldosteronism:*** the cause of excess aldosterone production resides with in the adrenal gland
   - ***Aldosterone producing adrenal adenoma (Conn's syndrome)***: in most cases , unilateral small adenoma which can occur on either side
   - ***Adrenal carcinoma:*** rare cause of aldosteronism
   - ***Bilateral cortical nodular hyperplasia /idiopathic hyperaldosteronism***

2. ***Secondary aldosteronism***: the stimulus for excess aldosterone production is outside the adrenal gland. It refers to a appropriately increased production of aldosterone in response to activation of the renin-angiotensin system
   - ***Accelerated phase of hypertension***
   - ***Pregnancy***
   - ***Congestive heart failure***
   - ***Other edema states : nephritic syndrome , CLD etc***

Pathophysiology: The excess aldosterone increase the reabsorption of sodium and excretion of potassium and hydrogen ions, in the distal renal tubules, which results progressive depletion of potassium and leads to hypokalemia.

Signs and symptoms:

- ***Moat patients have diastolic hypertension*** resulting from sodium retention. Patients may complain headache and symptoms of other organ damage
- ***Hypokalemia and associated symptoms***: muscle weakness and fatigue.
- ***Impairment of urinary concentrating ability***→polyuria and polydipsia.
- ***Metabolic alkalosis*** with paresthesia, possibly tetany

ECG:

- Evidences of left ventricular enlargement
- ECG signs of hypokalemia : prominent U waves and cardiac arrhythmias

Laboratory Diagnosis:

- ***Hypokalemia in hypertensive patients*** is often the clue that triggers the search for primary aldosteronism :
- ***Metabolic alkalosis***
- ***Serum aldosteron level***: elevated aldosteron and metabolites in 24-h urine
- ***Plasma renin activity***: is the most important useful indicator of whether elevated aldosterone is primary or secondary. Increased plasma renin activity favours the diagnosis of secondary aldosteronism. While raised aldosteron level with reduced plasma renin activity suggests primary aldosteronism.
- ***CT scan and MRI***: may detect aldosteron secreting adenomas.

Treatment:

1. ***Surgery:*** removal of solitary adenoma results cure of hypertension in about 60 % of cases and improvement in another 25 %. Adrenalectomy is done after 4 week treatment with spironolactone (in case of adenoma, hyperplasia)
   In contrast only 20%-50 % of patients with bilateral hyperplasia are improved with surgery, even if bilateral adrenalectomy is performed.
2. ***Medical Therapy: Spironolactone*** inhibits the effects of aldosteron on renal tubule.
   In idiopathic form: Spironolactone (50-100 mg/d), possibly combined with potassium-sparing diuretics correct the hypokalemia and with anti-hypertensive medication , high blood pressure can be controlled.

References:

3) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Disorders of the adrenal cortex , pages 2127-1508-1515
4) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Disorders of the adrenal gland, pages 492-501.

4. Diseases of the pituitary gland

1. **Anterior pituitary diseases may result from:-**
   - *i)* ***Insufficient production of pituitary hormones:*** hypopituitarism
   - *ii)* ***Excess production of pituitary hormones:***
     - *a. Acromegaly,*
     - *b. Cushing's diseases*
     - *c. Hyperprolactinoma*
   - *iii)* ***Local effect of pituitary tumours***

2. ***Posterior Pituitary diseases***

I) Hypopituitarism (Insufficient production of anterior pituitary hormones)

- Hyposecretion may be generalized (hypopituitarism) or caused by the selective loss of one or more pituitary hormones.

Generalized hypopituitarism

Definition: *Endocrine deficiency syndromes due to partial or complete loss of anterior lobe pituitary function.*

Etiology:

1. ***Pituitary tumours***
   - ***Chromophbic adenomas***
   - ***Craniopharyngioamas***
2. ***Infarction of ischemic necrosis of the pituitary***
   - ***Shock , especially post partum (Sheehan's syndrome) or in Debates mellitus or Sickle cell anemia***
   - ***Vascular thrombosis or aneurysm of the anterior cerebral artery***
   - ***Hemorrhagic infarction*** : pituitary apoplexy
3. ***Inflammatory /infectious process :*** meningitis (tuberculus) , pituitary abscess
4. ***Infiltrative diseases:*** Sarcoidosis , hemochromatois ,
5. ***Iatrogenic :*** irradiation or Surgical removal of pituitary tumours or during operation for other bran tumours

Clinical features:

- The onset is usually insidious and may not be recognized as abnormal by the patient, but occasionally it may be sudden or dramatic. The function of all target glands will decrease when all hormones are deficient **(panhypopituitarism).**
- ***With slow progressive destruction of pituitary tissue ,***
    - Failure of GH and gonadotrophin secretion occurs early
    - TSH failure comes next
    - ACTH level falls finally

1) Growth hormone deficiency

- In children growth failure
- In adults: increases adipose tissue and decreases lean body mass , leading to reduced strength and exercise capacity

2) Gonadotrphine (LH and FSH) deficiency :

- **In women**: amenorrhea and genital atrophy and infertility, if there is associated loss of adrenal androgens , because of concomitant ACTH, deficiency , pubic and axillary hair may be lost , in women
- **In men:** loss of potency and libido, testicular atrophy, regression of secondary sexual characteristics, and decreased spermatogenesis with consequent infertility

3) TSH deficiency: symptoms and signs of hypothyroidism

4) ACTH deficiency: leads to secondary type of adrenal insufficiency. This type of adrenal insufficiency differs from primary adrenal insufficiency in that :

- There is no hyperpigmentation of skin and mucous membrane
- Hyponatremia and Hypokalemia are minimal, since aldosteron production, which controls the balance of these electrolytes, mainly depends on the renin-angiotensin system.

5) Prolactine deficiency: postpartum failure of lactation

Pituitary apoplexy is a symptom complex caused by hemorrhagic infarction of either a normal pituitary gland or, more commonly, a tumor.

- Acute symptoms may include severe headache, stiff neck, fever, and visual disturbances.

- Varying degrees of hypopituitarism may develop suddenly, and the patient may present in vascular collapse because of deficient ACTH and cortisol secretion. Often the CSF is hemorrhagic.

Diagnosis:

1) **Evaluation of target organ function:** is often the first step in the diagnosis of hypopituitarism; this condition is often suspected because of failure o more than one target organ
    - ***Evaluation of thyroid function: T4, T3, TSH***
    - ***Evaluation of ACTH secretion***
    - ***Evaluation of prolactin levels***: prolactin not regularly depressed
    - ***Evaluation of serum LH and FSH levels***: helpful in postmenopausal women, not so much in others.
    - ***Measurement of GH hormone level:*** may be undetectable under baseline condition, provocative maneuvers are needed to prove inadequacy of hormone production
        - ***Insulin induced hypoglycemia/ Insulin tolerance***: test is the most consistent effective test : Regular insulin at a dosage of 0.1 U/kg body weight is given IV over 15 to 30 sec, and venous blood samples are obtained to determine GH, cortisol, and glucose levels at zero time (before insulin administration) and 30, 60 and 90 minutes later. The fall in serum glucose level is maximal at 30 minutes, is followed by a rise in GH level to a level greater than 8-10ng/ml n normal individuals. Blood cortisol level is also expected to rise. Failure to rise in the level of both hormones may suggest hypopituitarism.

2) Imaging studies

- Skull x-ray of sella turcica (detects macroadenomas > 10 mm)
- High-resolution CT or MRI if available

3) Formal visual field testing

Differential diagnosis:

- Anorexia nervosa,
- Chronic liver disease (alcohol, hemochromatosis),
- Polyglandular autoimmune disease

Therapy:

1) ***Treatment of the underlying cause the patients pituitary insufficiency***

Surgery:

- If hypopituitarism is due to tumor and tumor is small and is not secreting prolactin, most favour Transphenoidal removal of the neoplasm.
- Most endocrinologists consider bromocriptine the initial treatment of prolactinomas, regardless of size.
- With larger tumours and suprasellar extension, resection of the entire neoplasm, either transsphenoidally or transfrontally, may not be possible, and adjunctive irradiation may be needed.
- After surgical or radiation treatment, other hormones may be lost as well, and replacement may be needed accordingly.
- In pituitary apoplexy, Transphenoidal decompression of the often hemorrhagic tumor should be undertaken promptly

Medical: Treatment of granulomatous diseases

2) **Hormone replacement therapy** : treatment is directed toward replacing the hormones of the hypofunctioning target glands.

- **GH replacement**: given for children with growth failure
- **Thyroid hormone replacement**: given in usual replacement dose
- **Cortisol** is given in the usual replacement dose
- **Estrogens and progesterone combination**: may be given to women to restore menstrual function and Testosterone may be given to men to restore libido and potency

II) Selective pituitary hormone deficiencies

Definition: A clinical condition in which one or more pituitary hormones are deficient; may represent an early stage in the development of more generalized hypopituitarism so evaluate patient regularly.

Forms:

- **Isolated GH deficiency** is responsible for many cases of pituitary dwarfism.
- **Isolated gonadotropin deficiency** occurs in both men and women and must be distinguished from primary hypogonadism.

- **Isolated ACTH deficiency** is a rare clinical entity. Symptoms of weakness, hypoglycemia, weight loss, and decreased axillary and pubic hair suggest the diagnosis. Plasma and urinary steroid levels are low and rise to normal after ACTH treatment. Clinical and laboratory evidence of other hormonal deficiencies is absent.
- **Isolated TSH deficiency** is likely when clinical features of hypothyroidism exist, plasma TSH levels are not elevated, and no other pituitary hormone deficiencies exist. Plasma TSH levels are not always lower than normal, suggesting that the TSH secreted is biologically inactive.
- **Isolated prolactin deficiency** has been noted rarely in women who fail to lactate after delivery.

III) Hypersecretion of anterior pituitary hormones (hypopituitarism)

The anterior pituitary hormones that are most commonly secreted in excess are

- GH hypersectretion: which manifests as an Acromegaly or, gigantism
- Hyperprolactinoma:
- Excess secretion of ACTH : results as in the pituitary type of Cushing's syndrome

Gigantism and Acromegaly

Definition: *Syndromes of excessive secretion of GH (hypersomatotropism) nearly always due to a pituitary adenoma of the somatotrophs.*

Clinical features: excess GH secretion may cause changes in bone, soft tissue and metabolic process.

Bone and soft tissue changes:

1. **Gigantism:** GH hypersecretion beginning in childhood before closure of epiphyses may cause increase linear growth of long bones resulting gigantism. There is little bony deformity, soft tissue swelling or enlargement of peripheral nerves.
   Delayed puberty or hypogonadotropic hypogonadism may be present.
2. **Acromegaly:** GH hypersecretion beginning after epiphyseal closure, in adults, result soft tissue growth and bony enlargement, especially in acral areas of the skeleton, which may affect the patient's appearance.
   - ***Enlargement of hands*** (especially fingertips) and feet: increased ring, gloves and shoe size.
   - ***Coarsening of facial features***

- ***Thick skin folds***: brows and nasolabialfolds
- ***Enlargement of the nose***
- ***Enlargement of mandible:*** Prognathism, spreading of teeth

- ***Body hair increases and the skin thickens*** and becomes darker.
- ***Excessive perspiration***, offensive body odour may be noted.
- ***Voice becomes husky***, ***tongue enlarged*** and furrowed.
- ***Barrel chest deformity*** may be noted.
- ***Joint symptoms are common***, crippling degenerative osteoarthritis may occur.
- ***Galactorrhea*** may occur in women and menstrual irregularities/amenorrhea may be noted. ***Impotence*** is common in men.
- ***Peripheral neuropathies*** due to entrapment of peripheral nerves are common, as are headaches (due to pituitary tumor).
- ***Bitemporal hemianopsia*** (visual field defect) may develop due to the pressure effect of pituitary adenoma.
- ***Enlargement of internal organs:*** The heart, liver, kidneys, spleen, thyroid, parathyroid glands, and pancreas are also larger than normal. Cardiac disease in 1/3 of patients.

3. Metabolic changes:

Poor glucose tolerance, a result of the anti-insulin actions of GH, is common.

Over diabetes occurs in only 10% of acromegalic patients.

Diagnosis:

Diagnosis of Acromegaly depends on the clinical manifestations.

- ***GH level***: should be measured in the morning under basal condition.
- A level higher than 10ng/dl favors the diagnosis of Acromegaly.
- ***Glucose tolerance test:*** to diagnose for possible DM
- ***Skull x-ray:*** in most cases the pituitary adenoma is large enough to distort the sella turcica and can be seen on lateral skull x-ray
- ***CT or MRI (if available):*** will help to visualize the tumor.
- ***Other X-ray changes***: Enlargement of sinuses

  Tufting of distal phalanges, cortical thickening.

Treatment:

1. **Ablative therapy ;**
   - ***Transpheniodal pituitary adenomectomey :*** results prompt normalization of GH in the majority of patients
   - ***Irradiation therapy radiation*** is generally indicated, but be aware of danger of hypopituitarism.
2. ***Medical therapy*** is indicated if surgery and radiotherapy are contraindicated or have failed.
   - Give bromocriptine up to 15 mg/d PO in divided doses.

Hyperprolactinoma /Galactorrhea

Definition: Hyperprolactinoma is a clinical condition resulting from excess secretion of prolactin in men, or in women who are not breastfeeding.

Etiology:

1. ***Prolactin secreting pituitary adenomas (Prolactinoma),*** are more common in women than in men, usually appearing during reproductive years. Majority are microadenomas (< 10 mm in size). Men tend to have larger tumors (macroadenomas), which usually are suspected because of neurologic impairment and hypogonadism.
2. ***Damage to the hypothalamus or the pituitary stalk:*** by tumors , granulomas and other process may prevent the normal regulatory effect of hypothalamic dopamine on lactotrope activity , resulting hypersecretion of prolactin.
3. ***Drugs:*** drugs that inhibit dopamine activity, and thus interfere with its regulatory activity on prolactin secretion. Some of the drugs are phenothiazines, antidepressants, antihypertensives (methyldopa, reserpine), opioids, cimetidine, metoclopromide, contraceptives etc
4. ***Other rare causes :***
   - Primary hypothyroidism
   - Chronic liver disease
   - Renal failure
   - Ectopic prolactin production from tumors (paraneoplastic syndromes)

Clinical features:

In women:

- ***Galactorrhea:*** is the direct result of prolactin excess.
- ***Amenorrhea or menstrual irregularity*** is due to inhibition of hypothalamic GnRH production by prolactin as well as the direct effect of prolactin on the ovaries.
- ***Signs of estrogens deficiency*** may be seen such as hot flushes and dyspareunia.

In men:

- ***Loss of libido and potency***, hypogonadism.
- ***Headaches, visual difficulties*** result from the compression effect of tumors, which are often larger in men.

Diagnosis:

- ***Prolactin levels***: are elevated. A serum prolactin level greater than 300ng/ml strongly suggests the presence of prolactinoma. Functional causes such as drugs seldom elevate the prolactin level above 100-200ng/ml
- ***Skull x-ray (lateral):*** CT/MRI: are used to visualize the adenoma.
- ***Visual field examination***

Therapy:

Depends on the size of the tumor, and its manifestation.

1. **Surgical therapy: transsphenoidal surgery**: cures most patients with small adenomas.
2. **Medical:** ***Bromocriptine*** is remarkably effective in decreasing prolactin level, usually, to normal. It also reduces tumor size.

   Dose: initial dosage 1.25 mg once or twice daily may need to be increased to 10-20mg daily for full effect.

   Side effects: headache, dizziness, fatigue.

   Larger tumors with suprasellar extension are not cured by surgery. Such macroadenomas may be initially treated with bromocriptine. If the tumor shrinks, there is a greater chance for successful surgery.
3. ***Radiotherapy*** is reserved for therapy-resistant cases. It may be used in conjunction with surgery and bromocriptine to further reduce tumor size and function.

IV) Posterior Pituitary lobe Disorders

Central Diabetes Insipidus

Definition: A temporary or chronic disorder of the neurohypophyseal system due to deficiency of vasopressin (ADH), and characterized by excretion of excessive quantities of very dilute (but otherwise normal) urine, and by excessive thirst.

ADH is produced by cells in the supraoptic and paraventricular nuclei of the hypothalamus, travels down through the pituitary stalk and stored in the posterior lobe of the pituitary gland (neurohypophysis)

Etiology:

1. ***Primary/Idiopathic***: account for approximately 50 % of the cases of diabetes insipidus.
2. ***Injury to the hypothalamus* –pituitary *area:*** may result from head trauma, neurosurgical procedures such as hypophysectomy.
3. ***Less common causes***: neoplasms, histiocytosis, granulomas, vascular lesions, infections (encephalitis.)

Clinical features: Onset insidious or abrupt; may occur at any age.

- **Polyuria:** with urine volume f 3-15 L daily, result from the inability to reabsorb free water and to concentrate urine. Nocturia is almost always present, which may disturb sleep and cause mild day time fatigue or somnolence.
- ***Thirst (polydipsia)***: leads to increased fluid intake. A conscious patient with normal thirst mechanism and free access to water will maintain hydration. However rapid and life threatening dehydration and hypovolemia may develop rapidly, if urinary losses are not continuously replaced, which may occur in unconscious patients or infants.

In primary DI, only polydipsia and polyuria are present.

In acquired DI, signs and symptoms of associated lesions are also found.

Diagnosis:

1. **Measurement of plasma osmolality:** in untreated patients helps to distinguish the cause of polyuria. In DI, the loss of free water leads to high osmolality (280-310 mOsm/kg). In psychogenic polydipsia excess fluid intake is primary and serum osmolality is low (255 - 280 mOsm/kg)

2. **Water deprivation test:** started in the morning by weighing the patient, obtaining venous blood to determine electrolyte concentrations and osmolality, and measuring urinary osmolality.

   Fluid intake is withheld, and voided urine is collected hourly and its osmolality is measured. Dehydration is continued until

   - Orthostatic hypotension and postural tachycardia appear,
   - 5% or more of the initial body weight has been lost, or
   - The urinary concentration does not increase by more than 30 mOsm/L in sequentially voided specimens for 3 hrs.

   At this point, serum electrolytes and osmolality are again determined, and

   Five (5 U) of *aqueous* vasopressin or 2 µg of desmopression is then injected SC.

   Urine osmolality is measured 1 hr later.

Table VII-4- 2 Interpretations of Water deprivation test

Disorder	***Urinary osmolality in response to water deprivation***	***Response to Vasopressin injection***
Normal response	Urinary osmolality increases > 280 mOsm/kg	No further increment in urine osmolality
Central DI	The urinary osmolality does not increase	Urinary osmolality increases
Nephrogenic DI	The urinary osmolality does not increase	The urinary osmolality does not increase

3. **Measurement of circulating ADH concentrations by radioimmunoassay**

Differential diagnosis:

- **Compulsive (psychogenic) water drinking**
- **Nephrogenic diabetes insipidus.**

Treatment:

1. **Hormonal therapy:**

- ***Aqueous vasopressin SC or IM in doses of 5-10 U.*** Since effect lasts 6 h or less, use in chronic treatment is limited.
- ***Desmopresin:*** DDAVP (synthetic vasopressin) in a dose of 0.05-0.2ml applied to the upper respiratory mucous membrane twice daily by nasal cannula or nasal spray.

  The effect lasts 12-24 h, can be given intranasally, SC or IV and it is a preparation of choice for both adults and children.

2. **Nonhormonal therapy:** to reduce polyuria
   - ***Chlorpropamide*** (an oral hypogycemic agent) may increase endogenous ADH in patients who have partial ADH deficiency.

     Dose: 250-500 mg PO makes patients asymptomatic daily 3-5 mg/kg PO.
   - ***Thiazide diuretics***: have paradoxical effect on decreasing urine output in patients with DI. They are the preferred drugs for treating nephrogenic DI.

     Thiazides are only partially effective, decreasing the urine volume by 30%-50 %.
   - ***Restricting salt intake*** may be helpful.
   - Prostaglandin inhibitors such as indomethacin (1.5-3 mg/kg/d PO in divided doses) may be effective.
   - Treatment of underlying causes of DI , if treatable.

References

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Disorders of the anterior Pituitary and the neurohypophysis, pages 2076- 2103.
2) Myers R. Allen , National Medical Series for independent Study (NMS) 3rd edition Medicine, Diseases of the pituitary gland, pages 75-78

CHAPTER EIGHT

DISEASE OF THE NERVOUS SYSTEM

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Understand the epidemiologic significance of Headaches.*
2. *Understand the classification of common headaches.*
3. *Identify the clinical manifestation of common headaches.*
4. *Manage patients with acute common headache and prevention of recurrent attacks.*

1. Headache

- Headache is one of the commonest complaints in medical practice. As many as 90% of individuals have at least one episode of headache per year. Severe disabling headache is reported to occur at least annually by 40% of individuals worldwide.
- It results from distention, stretching, inflammation or destruction of pain sensitive cranial structures. These pain sensitive structures are the scalp, dura, sinuses, falx cerebri, middle meningeal arteries, proximal segments of large pial arteries and cranial nerves 5, 9 and 10. Brain parenchyma is not pain sensitive.
- A pain (sensory stimuli) from these structures is conveyed to the brain either via trigeminal nerve or first three cervical nerves.

Classification of headaches

Headache can be clarified pathophysiologically as:

1. ***Vascular headache***
   - Migraine headache
   - Cluster headache
   - Miscellaneous (orgasmic, Hangover)
2. ***Cranial Neuralgias***
3. ***Tension headache***
4. ***Traction –inflammation headache***
   - Cranial arteritis
   - Meningitis
   - Brain tumor
   - Increased /Decreased ICP

5. ***Extra cranial lesions***
    - Paranasal sinusitis
    - Dental problems
    - Ear problems
    - Ocular problems
    - Cervical problem

Evaluation of patients presenting with Headache

When evaluating a patient with headache, the goal is to:

- Distinguish serious headache from benign headache syndrome
- Give appropriate treatment.

Appropriate History is critical in evaluating a patient with headache.

- ***Characterize the headache:*** the quality, location, duration, time course, the conditions that produce, exacerbate or relieve it should be reviewed.
- ***Look also for associated symptoms, medication history and psychiatric history.***

Physical Examination: is important to search for underlying serious illnesses. It should include

- ***Vital signs*** (Blood pressure, temperature)
- ***Head and neck examination***: scalp tenderness, sinus tenderness, examination of the oral cavity and tempromandibular joint.
- ***Ophthalmologic evaluation including*** : fundoscopic examination pupillary size, corneal clouding
- ***Systematic evaluation of other systems*** (Glands, chest, CVS, abdomen, GUS, MSS, and Integumentary system)
- ***Neurological examination*** including change in mental status, focal neurological deficit, neck stiffness and other meningeal signs

Investigation

- Diagnosis of common primary headache syndromes is clinical. No specific test is available.
- Occasionally investigations including Neuro-imaging studies are important if the headache is atypical or it is associated with abnormalities on physical examination.

After appropriate evaluation of the headache the following clinical features should be considered as indicators of serious underlying disease.

1. First severe headache ever described as the worst type of headache in the patient's life may suggest subarachnoid hemorrhage

2. Subacute worsening over days or weeks (tumor)
3. Disturbs sleep or present immediately upon awakening (tumor)
4. Abnormal neurological exam (space occupying lesions)
5. Fever or other unexplained systemic signs (meningitis)
6. Vomiting precedes headache
7. Headache induced by bending, lifting or cough
8. Known systemic illnesses
9. Onset of headache in patients older than 55 yrs.

Common Headache syndromes

1. Vascular headache

- Vascular headaches refers to a group of headache syndromes, of unknown cause ,in which pain results from dilation of one or more of branches of carotid arteries.
- Migraine headache and cluster headache account for the majority of the cases.

A) Migraine Headache

- ***Definition:*** migraine headache is a benign and episodic disease, characterized by headache, nausea, vomiting and/ or other symptoms of neurological dysfunction.
- It is the most common cause of vascular headache. It approximately affects 15% of women and 6% men.
- It usually begins in childhood or young adult life.

Etiology: the cause of migraine is often unknown, but several common precipitants have been observed.

1) ***Family history*** of migraine present in nearly 2/3 of patients.
2) ***Environmental, dietary and psychological factors.***
    - Emotional stress , depression
    - Altered sleep pattern or sleep deprivation
    - Menses , Oral contraceptives
    - Alcohol intake especially red wine
    - Caffeine withdrawal
    - Various food staffs (e.g. . chocolates, nuts, aged , cheese , meals containing nitrates

- Perfumes

3) It may develop after seemingly minor head injury.

Pathogenesis: different hypothesis are proposed including:

1) ***Vascular theory:*** in this theory it is said that migraine and neurological symptoms are results of extracranial vasodilatation and intracranial vasoconstriction.
2) ***Neuronal theory***: a slowly spreading neuronal depolarization is considered as a cause.
3) ***Trigeminovascular system abnormality***: this theory says dysfunction of trigeminal nucleus caudalis leads to release of vasoactive neuropeptides resulting in migraine.

Clinical feature

Migraine may be precipitated by some of the factors mentioned above. It is relieved by sleep and exhilaration, Sumatriptan and pregnancy.

The syndrome of Classical migraine has five phases:

- ***Prodromal phase***: characterized by lassitude, irritability difficulty in concentrating
- **Aura phase:** patients with aura often report visual complaints, vertigo, aphasia or other neurological deficit before the onset of the headache
- ***Headache phase*** – characteristic migraine headache
- ***Headache termination*** – usually occurs within 24 hours
- ***Post headache phase*** – feeling of fatigue. Sleepiness and irritability

Characteristic Migraine head ache is:

- Moderate to severe head pain , pulsating quality often unilateral (affecting half part of the head)
- It is exacerbation by physical activity and relived by sleeping
- It is often associated with Nausea and/or vomiting, photophobia, phonophobia/ sonophobia (dislike ad avoidance of laud sounds or noises).
- Multiple attacks may occur, each lasting 4 – 72 hrs.

There are different variants of Migraine

Common migraine

- This is the commonest variation of migraine headache
- No focal neurological disturbance precedes the recurrent headache

Classic migraine

- It is associated with characteristic premonitory sensory, motor or visual symptoms. Most common symptoms reported are visual which include scotomas and/or hallucinations.

Complicated migraine

- Migraine associated with dramatic transient neurological deficit, or a migraine attack that leaves a persisting residual neurological deficit.

Treatment

Therapy should first involve removal of inciting agents when possible.

1. Acute/abortive treatment of migraine

These are lists of drugs effective for acute management of migraine attack

a) **NSAIDS (Nonsteroidal antinflamatory agents):** such as ASA, paracetamol, Ibuprofen, Diclofenac may reduce the severity and duration of migraine attack. These drugs are effective for mild to moderate attacks and are most effective when taken early.
   Side effects: Dyspepsia and GI irritation are common side effects.

b) **5-Hydroxytryptophan-1 Agonists:** is a serotonin agonist that decreases substance P release at the trigeminovascular junction.

   i. **Nonselective (Ergot preparations: Ergotamine and dihydro-ergotamine)**
      - o Widely used for relief of acute attacks
      - o Has oral, sublingual, rectal, nasal and parentral preparation. Parentral forms are used for rapid relief of the attack.
      - o Usually prepared combined with caffeine which potentiates the effect by improving absorption.
      - o ***Dose: Initial*** dose: 1 – 2 mg oral /SL/ rectal and repeat every hour if there is no relief of headache to a maximum of 6 – 8 mg over 24 hrs
      - o ***Side effects:*** are nausea, vomiting, myalgias, chest discomfort, peripheral ischemia and even angina. Excess use may lead to rebound headache and dependency
      - o ***Contraindication:*** patients with vascular diseases like coronary heart disease

   ii. **Selective - Triptans including** (Naratriptan, Ritatriptan, Sumatriptan, and Zolmitriptan): are new drugs in management of migraine.
      - o ***Sumatriptan –*** single 6 mg SC dose is effective in 70 – 80% of patients

c) **Dopamine agonists:** are used as adjunctive therapy.

2. ***Prophylactic Treatment:*** includes drug regimens and changes in patients behavior

Medical therapy:

- These are drugs that have capacity to stabilize migraine. Prophylactic treatment is indicated if the patient has three or more attacks per month.
- Drugs used for this purpose include β-blockers (propranolol), Tricyclic antidepressants (amitriptyline), and Calcium channel blockers (Verapamil), Valproic acid.
- Start with low dose and gradually increase if there is no adequate response.

Biofeedback therapy

- It is simple and cost effective. It lessens migraine attacks by helping patients deal more effectively with stress

B) Cluster Headache

- Cluster head ache is a vascular headache syndrome, characterized by severe, acute headache that occurs in clusters lasting several weeks followed by pain free intervals that averages a year.
- Common in men than women. Male: Female ratio is 8:1
- Usually begins 3rd to 6th decades
- Cluster headache is periorbital less commonly temporal. It has rapid onset without warning. It is also severe and explosive in quality lasting 30 min to 2hrs, subsiding abruptly.
- Clusters characteristically occur in the spring and fall several times a day particularly at night and stay for 3 – 8 weeks
- During attack patients often have associated nasal stiffness, lacrimation and redness of the eye ipsilateral to the headache.
- Alcohol provokes attacks in about 70% of patients

Treatment

Acute attack /abortive therapy (Treatment)

- Inhalation of 100% oxygen and
- ***Sumatriptan*** 6 mg S.C. stat said to be helpful and ergotamine or other analgesics may also be used.

Preventions/prophylactic therapy: clusters attacks can be prevented effectively by:

- Prednisolone , Lithium, Methysergide, Ergotamine, Sodium valproate and verapamil

C) Tension headache (Tension type headache)

- Most common cause of headache in adults
- Common in women than men
- Can occur at any age, but onset during adolescence or young adulthood is common.

Etiology: various precipitating factors may cause tension headache in susceptible individual including.

- Stress – usually occurs in the afternoon after long stressful work hours
- Sleep deprivation
- Uncomfortable stressful position and/or bad posture
- Hunger (Irregular meal time)
- Eye strain resulting from continuous TV watching, working on computer screen for a long time.

Clinical feature

- Tension headache is characterized by mild or moderate, bilateral pain. Headache is a constant, tight, pressing or band like sensation in the frontal, temporal, occipital or parietal area.
- Usually lasts less than 24 hrs but can persist for days or weeks.
- Prodromal symptoms are absent some patients have neck, jaw or tempromandibular joint discomfort.
- On examination some patients may have tender spots in the pericranial or cervical muscles.

Treatment: management of tension headache consists:-

1. ***Pharmacotherapy***
   - **Abortive therapy/acute treatment**
     - Stop or reduce severity of individual attacks
     - This can be done with simple analgesics like paracetamol, ASA, Ibuprofen, and Diclofenac. If treatment is unsatisfactory addition of caffeine or other analgesic is beneficial.

- **Long term preventive therapy**
    - Main form of therapy for chronic form of tension headache
    - This kind of treatment is indicated if the headache is :
        - Frequent (> 2 attacks / week),
        - Of long duration (> 3hrs)
        - Severe (cause significant disability)
        - Associated with overuse of abortive medication
    - Commonly used drug for long term treatment is Amitryptilline.

2. *Physical Therapy:* different techniques can be used including

- Hot or cold application
- Positioning
- Stretching exercises
- Traction
- Massage

3. Psychological Therapy

- Includes reassurance, Counseling, relaxation, stress management programs and biofeedback techniques reduce both the frequency and severity of chronic headache.

D) Headache Associated with Brain Tumor

- About 30% of patients with brain tumor present with headache.
- Brain tumor can affect all ages and both sexes. Headache of brain tumor is usually intermittent dull aching, moderate intensity which worsens with time. It disturbs sleep in about 10% of patients, exacerbated by exertion and postural changes. With time patients can develop nausea and vomiting.
- Upon examination focal neurological deficit may be detected.

E) Temporal Arteritis

- It is also called giant cell arteritis. It is an inflammatory disorder of the carotid artery and its branches.
- It is common in elderly, and women account for 65% of cases.

Clinical feature

- Typical presenting symptom includes headache, polymyalgia rheumatica, jaw claudication, fever and weight loss.

- Headache is located to temporal or occipital area, described as dull and boring. It is usually worse at night and is often aggravated by exposure to cold.
- Scalp tenderness is often found over temporal artery.
- 50% of patients with untreated temporal arteritis develop blindness due to involvement of ophthalmic artery and its branches.

Diagnosis

- ESR is often elevated.
- Biopsy of temporal artery confirms the diagnosis.

Treatment

- Prednisolone 80 mg /day for 4 – 6 weeks

F) Lumbar Puncture headache

- Occurs in 10 – 30% of patients having LP
- Usually begins within 1 – 2 days and persists for 3 – 4 days.
- Headache of lumbar puncture is usually bifrontal or occipital, dull aching aggravated by sitting or standing, head shaking, jugular vein compression and disappears in prone or supine position.
- ***Treatment:*** simple analgesics and lie the patient supine.

References:

3) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Headache, pages 85-93.
4) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Headache, pages 61—613.

2. Diseases of the Spinal cord

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Identify the characteristic features of diseases of the spinal cord.*
2. *Describe the Etiologies of diseases of the spinal cord.*
3. *Identify the clinical manifestation of common diseases of the spinal cord.*
4. *Understand the diagnostic wok up for common diseases of the spinal cord.*
5. *Understand the management of common diseases of the spinal cord.*

- Spinal Cord is part of the central nervous system contained in the spinal canal. The adult spinal cord is 18 cm long, oval or round in shape in cross section. It has two parts, white matter and gray matter, with central canal at the center. The white matter contains ascending sensory and descending motor fibers and gray matter contains nerve cell bodies. Spinal cord is organized into 31 somatotropic segments, i.e. 8 cervical, 12 thoracic, 5 Lumbar, 5 sacral and 1 coccygeal segments.
- Diseases of the spinal cord are frequently devastating, because the spinal cord contains, in a small cross-sectional area, almost the entire motor output and sensory input of the trunk and the limbs.

Generally diseases of spinal cord are characterized by:

- ***The presence of a level below which motor/sensory and/or autonomic function is disturbed.***
    1. ***Motor disturbance*** causes weakness (paraplegia, quadriplegia), spasticity, hypereflexia and extensor plantar response, which is due to disruption of descending corticospinal fibers.
    2. ***Impaired sensation*** results from disordered function of ascending spinothalamic and dorsal column pathways.
    3. ***Autonomic disturbance*** leads to disturbed sweating, bladder, bowel and sexual dysfunction.

Some causes of spinal cord diseases

1) ***Compressive*** : lesions may be epidural, intradural or intramedullary
    i) TB spodylitis
    ii) Neoplasms
    iii) Epidural abscess
    iv) Epidural hemorrhage
    v) Cervical spondylosis
    vi) Herniated disc /disc prolapse
    vii) Fractured / displaced vertebral body
2) ***Vascular***
    i) AV – malformation
    ii) Spinal artery thrombosis or embolization
3) ***Inflammatory***
    i) Transverse myelitis, Borrelia, Syphilis
    ii) MS (multiple sclerosis)
    iii) Vasculitis
4) ***Infections***
    i) Viral : Varicella zoster virus , HSV-1 and HSV-2 , CMV , HIV
    ii) Bacterial : Myocobaterial ,
    iii) Parasitic : Schistosomaisis , Toxoplasmosis
5) ***Developmental :*** syringomyelia , meningomyelocel
6) ***Metabolic***
    i) V-B 12 deficiency
    ii) Neurolathrism: that is a spastic paraparesis resulting from consumption of “Guaya”, which grows in the northern part of Ethiopia. This cereal has neurotoxin which causes paraparesis when consumed in large amount for relatively long period of time.

Common Spinal Cord Diseases

A. Neoplastic spinal cord compression

May be classified as:

1) ***Extramedullary:*** tumor outside the spinal cord.
    i) ***Epidural:*** outside the dural layer

- Commonest cause of neoplastic compression of spinal cord in adults. Usually results from metastasis to adjacent vertebral bone or direct compression of the spinal cord.
- Commonest neoplasm include: breast, lung, prostate, kidneys, lymphoma and multiple myeloma
- Most frequently involved site is thoracic cord

ii) ***Intradural:*** inside the dural layer

- These are slowly growing benign tumors like meningioma, neuroblastoma, lipoma

2) ***Intra medullary:*** tumors within the spinal cord.

- These are uncommon tumors , including ependymoma, hemangioblastoma low grade astrocytoma

Clinical feature

- Initial symptom is backache, which is localized, and which worsens with movement, coughing or sneezing. The pain may radiate to the legs, trunk or following dermatomal distribution.
- The pain may be sever and awaken the patient at night.
- As compression progresses patient develops progressive weakness, sensory abnormalities and autonomic disturbances change in bladder function and constipation.

Physical findings include:

- Weakness, spasticity, hyperreflexia
- Loss of or decreased sensations to pinprick in the lower extremities
- Extensor plantar response , and loss of abdominal reflexes and anal sphincter tone
- Urinary retention

Investigations

- Check for primary tumor sites
- Plain X-ray of the spine
- Myelography
- Radionuclide bone scan
- CT/MRI
- Biopsy → usually unnecessary in patients with known pre-existing cancer.

Therapy: depends on site and type of tumor.

Treatment modalities include

Steroids: help to reduce the interstitial edema

Should be started immediately with in the first 12 hrs of occurrence of symptoms

Prednisolone 40 mg PO BID , or Dexamethason 12 mg IV followed by 4 mg IV QID may be used

Radiotherapy.

Is effective even for classically radio-resistant tumors

Prevents new weakness and may give recovery of function

Surgery: decompression or vertebral body resection

Useful especially for intradural and intramedullary tumors

Note: Treatment should be started as soon as possible (with in 12 hrs). Fixed motor deficits (paraplegia or quadriplegia), once established for > 12 hrs, do not usually improve, and beyond 48 hrs the prognosis for substantial motor recovery is poor.

B. Tuberculosis of the spine (Pott's disease)

- One of commonest causes of myelopathy in developing countries where Tuberculosis is endemic, Ethiopia.
- Often Involves two or more adjacent vertebral bodies
- Commonest site is lower thoracic and upper lumbar vertebrae

Clinical features

- Patients present with insidious on set of back pain, which progressively get worse.
- Gibus deformity (kyphotic swelling over the back)
- Numbness and loss of sensation with a sensory level
- Weakness of the lower limbs, often spastic in nature, with exaggerated deep tendon reflexes and up going plantar (Babinisky's sign)
- Bladder and /bowel dysfunction (Urinary retention with overflow incontinence, constipation or fecal incontinence)
- In about 65% of cases evidences of extra spinal tuberculosis is present

Diagnostic workup:

1. **Imaging studies**
   - Plain radiograph show characteristically destructive process of the vertebrae, involvement of disc space with deformity.
   - CT/MRI may show the lesion more clearly

Treatment

- ***Medical Therapy***
  - ***DOTS: short course anti tuberculosis chemotherapy*** is mainstay of therapy.
  - ***Steroids*** can be added it there is neurological deficit
- ***Surgery:*** is indicated if there is spinal instability or deformity and unresponsiveness to medical treatment.

C. Prolapse of intervertebral disc

- It occurs due to trauma, sudden severe strain or degenerative changes.
- Commonest site of for disc prolapsed is the lumbar region.

Clinical feature

Localized back pain aggravated by straining with or without

- Radiculopathy
- Segmental sensory loss
- Changes in deep tendon reflexes (asymmetrical)

Straight leg raising sign is positive: the patient will have back pain, when stretched leg is raised / flexed at the hip joint.

Diagnostic workup

- Myelography: may help to localize the site of prolapse
- CT/MRI: can easily demonstrate the prolapsed disk

Therapy:

Medical therapy: is often supportive ad include

Bed rest, adequate analgesics and physical therapy

Supporting belts or corsets

Surgery: is the definitive treatment for disk prolapse.

D. Transverse Myelitis

It is an acute or sub acute inflammatory disorder of the spinal cord.

It occurs associated with;

- Antecedent infection (*either viral or Mycoplasmal*.)
- Recent vaccination
- Multiple sclerosis
- Collagen vascular disease (SLE)

Clinical feature

- Initial symptom is localized back or neck pain or radicular pain followed by various combinations of paresthesia, sensory loss, motor weakness and sphincter disturbances, which can evolve within hours to several days.

Investigation

- CSF: may be normal or show pleocytosis and increased protein.

Treatment

- Steroids can be used in moderate to severe cases.

E. Metabolic and toxic myelopathies

i) Subacute combined degeneration of spinal cord

- Neurologic disease mainly affecting the spinal cord, resulting from severe Vit-B_{12} deficiency.
- Vit-B_{12} deficiency results abnormalities on myelin basic protein leading to swelling of myelin sheath followed by demyeliniation and gliosis.
- These changes mainly affect the posterior and lateral columns of spinal cord.

Clinical Feature: patients present with;-

- Paresthesia in the hands and feet.
- Early loss of position and vibration senses (loss of propioreceptor sensations).
- Progressive spastic and ataxic weakness
- Some patients may develop optic atrophy and encephalopathy

Treatment

Vitamin B_{12}: 1000μg IM/d for 5 – 10 days, followed by
1000 μg IM/week for 1 month, and then
1000 μg IM month lifelong.

iii) Neurolathrism

- Neurolathrism is syndrome that affects the nervous system of man due to consumption of peas of the lathyrus species (“Guaya” seeds) that contains neurotoxic amino acid. Excessive consumption of these (Guaya) seeds occurs during times of food shortage, in Northern parts of Ethiopia (Gondar, Tigray, Wello and part of Gojam).

- It affects predominantly young men.

Clinical feature

Onset can be acute /subacute usually precipitated by manual labour, febrile illness or diarrhea then the patients will develop weakness, spasticity and rigidity progressively preventing them from walking. Usually no sensory abnormality is seen. Some of severely affected cases may develop incontinence and impotence.

Investigation

- No specific laboratory test required.
- Diagnosis of neurolathrism is by exclusion of other causes and taking proper dietary history and understanding the geographic distribution of the diseases.

Treatment

- No cure once established

Prevention

- Banning cultivation and consumption of the seed (" Guaya").
- Breeding of nontoxic variant if possible.
- Use of certain preparation methods (Cooking or soaking in excess water) makes the seed less toxic.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Diseases of the Spinal cord, pages 2438-2446.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Myelopathy and other spinal cord disorders, pages 635-637.

3. Cerebrovascular diseases

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define cerebrovascular diseases/stroke.*
2. *Understand the epidemiologic significance of stroke.*
3. *Understand the classification of stroke and the etiologies.*
4. *Identify the clinical manifestation of different types of stroke.*
5. *Understand the diagnostic approach of patients with stroke.*
6. *Understand the principles of management of patients with stroke.*
7. *Understand the preventive strategies for stroke.*

Definition: Syndrome of an abrupt onset of nonconvulsive, focal neurologic deficit resulting from sudden interruption of the blood supply to parts of the brain, lasting 24 hours or longer.

Classification of stroke

I. Etiologic classification

1) **Ischemic** -stroke accounts for 80 – 90% of all stroke in developed countries
   a) Embolic
   b) Thrombotic
      i) Large vessel disease: resulting from narrowing of cerebral arteries doe to atherosclerosis.
      ii) Small vessel disease (Lacunar infarct)
      iii) Miscellaneous: E.g. Vasculitis resulting thrombus formation
2) ***Hemorrhagic Stroke:*** accounts for 10-20 % of cerebrovascualr accidents in developed nations. It is a much more commoner cause of stoke in developing countries , mainly associated with unrecognized or poorly controlled hypertension
   a) Primary Intracerebral Hemorrhage (PICH)
   b) Subarachnoid Hemorrhage (SAH)

II. Classification based on the duration of stroke

1) ***Transient Ischemic attack:*** TIAs are focal neuralgic deficit lasting < 24 hrs confined to an area of brain perfused by specific artery , and neurologic deficit resolves in less than 24 hours

2) ***Reversible Ischemic neurologic deficit:*** sudden onset focal neurologic deficit which lasts for more than 24 hours, but the neurologic deficit recovers / resolves /.

3) ***Stroke in evolution:*** *a* focal neurologic deficit, the degree of which is progressing over a couple of hours or days.

4) ***Complete stroke:*** sudden onset of focal neurologic deficit, in which the deficit neither improves nor gets worse over time. It is often associated with infarction of part of the brain.

Epidemiology and risk factor

Stroke is prevalent all over the worldwide. It is third commonest cause of death in developed world following Coronary heart diseases and cancer. It is a leading cause of disability.

The prevalence and incidence of stroke is also on the rise in developing countries.

Major risk factors associated with stroke include

- *Incidence is higher in men and old age*
- *Hypertension*
- *Smoking*
- *Diabetic mellitus*
- *Hyperlipidemia*
- *Atrial fibrillation*
- *Myocardial infarction*
- *Congestive heart failure*
- *Acute alcohol abuse*

Approach to a patient with stroke:

Goals /Steps

1. Assessment and maintenance of vital functions
2. Determination of presumptive diagnosis of stroke subtype
3. Confirmation of stroke subtype
4. Management of a patients with stroke

1. Initial Assessment and maintenance of vital functions/stabilizing the patient

Stroke should be considered as medical emergency, as it affects vital functions of an individual. For this reason the initial step in management of patients with acute stroke should be rapid assessment and maintenance of vital functions. This includes:

a) Maintenance of air way and ventilation

b) Control of blood pressure

- Acute stroke alters autoregulation of cerebral blood flow, compromising the blood supply to an already damaged brain. Close monitoring of blood pressure and correction of both hypotension and hypertension reduces this risk.
- If the patient is hypertensive treatment is recommend only when the DBP ≥120 and SBP ≥ 200 mmHg. Short acting antihypertensive drugs are preferred.
- If the patient is hypotensive, it should be corrected by fluid administration and treatment of the underlying cause for the hypotension.

c) Control of body temperature.

- Fever occurs in 44% of patients with acute stroke. The fever may be due to stoke or infections. Because fever worsens the prognosis of stroke body temperature should be controlled appropriately.

d) Fluid management

- Maintenance of euvolumic state and establishment of IV access using normal saline (rather than glucose solutions) is also important. Glucose is said to be neurotoxic and it is better avoided in patients with stroke.

N.B Exclude causes of brain dysfunction, which mimic stroke like states like syncope, migraine, hysteria and trauma.

2. Determine Presumptive Diagnosis of Stroke Subtype

Numbers of clinical features are useful in determining the type of stroke. A good history taking, and proper physical examination may suggest the possible cause of the stroke.

Important historical information includes:

- ***Mode of onset and pattern of progression***
  - Embolisms usually occur suddenly when the patient is awake, most often early in the morning, giving maximum deficit at onset.
  - Hemorrhagic stokes also occur suddenly while the patient is awake, any may be physically active or straining, and progresses within minutes to hours.
  - Thrombosis often occurs during sleep hour or present upon arising from bed progressing in a stepwise fashion.
- ***Prior history of TIA*** (transient ischemic attacks). These are often associated with thrombotic (atherosclerotic) vascular disease.

- ***Associated symptoms***
    - Headache, vomiting, reduced alertness suggest hemorrhagic stroke than ischemic stroke. Very severe headache with altered consciousness without major neurologic deficit may suggest subarachnoid hemorrhage.
    - If patient is having fever raises suspicion of infective endocarditis.
    - Seizure is common in embolic stroke.
- ***Look for risk factors for stroke***
- ***Looking for other medical conditions*** associated with stroke such as hypertension, diabetes, smoking and use of drugs like OCP* may suggest the diagnosis.

Physical Examination

- Physical Findings may give clue to the type of stroke the patient is suffering from.
- Absent/reduced peripheral pulses suggest atherosclerosis or embolism
- Presence of neck bruit suggests extra cranial occlusion of carotid arteries
- Cardiac abnormalities: such as atrial fibrillation, murmurs or cardiac enlargement may suggest embolic stroke, the embolus originating from the heart.
- Fever raises concern for infectious etiologies
- Ophthalmoscopic examination: papilledma or retinal hemorrhage may suggest subarachnoid hemorrhage or increased intracranial pressure.

Table VIII-3-1. Characteristic features of different types of stroke

	Embolic stroke	***Intracerebral hemorrhage***	***Large vessel thrombosis***	***Lacunar infarctions***	***Subarachnoid hemorrhage***
Onset	Sudden onset with maximum deficit at onset	Sudden (deficit Progresses over minutes to hours)	Sudden, Gradual, stepwise, or Stuttering	Sudden, Gradual, Stepwise or Stuttering	Sudden, Usually few or not focal signs
Time of occurrence	When the patient is Awake	When the patient is Awake and active	When the patient is Asleep or inactive	When the patient is Asleep or inactive	When the patient is Awake and active

Warning signs (TIA)	None	None	Usually	Variable, TIA's may occur	None
Associated symptoms (Headache Vomiting)	Sometimes	Usually	Sometimes	No	Always (stiff neck)
CT scan	Decreased density	Increased density	Decreased density	Usually normal	Usually abnormal
LP	Usually clear	Usually bloody	Clear	Clear	Invariably blood

These characterizations are generally accepted principles regarding stroke; however, it is good to remember that stroke can present atypically.

3. ***Confirmation of Diagnosis:*** different investigations are needed to confirm the diagnosis.
   - ***Imaging studies (CT or MRI):*** are the most important initial diagnostic tests in patients with stroke (if available and affordable by the patient). CT can identify or excludes hemorrhagic stroke and other conditions which simulate stroke (like Neoplasm and abscesses). Complete Infarction is usually seen after 24 hours. MRI is more sensitive than CT for early diagnosis of brain infarction.
   - **Other Tests are:**

   Lumbar puncture – may be needed to make a diagnosis of small SAH which can be missed by CT or MRI.
     - Carotid Doppler studies : to look for carotid artery narrowing
     - Angiography : to identify the exact location and the specific artery blocked
     - Echocardiography : to look for cardiac sources of embolization
     - ECG: to look for arrhythmias such as atrial fibrillation

- CBC, ESR, VDRL
- Tests for HIV infection : stroke associated with vasculitis is common in HIV positive patients
- FBS, Lipid profile : to look for diabetes and hyperlipidemia 9 risk factors for stroke
- Coagulation profile: to look bleeding tendencies.

4. Management of specific stroke

Goal of Treatment

- Interruption of further brain damage
- Prevention and management of complication

A. General Measures

- Admit the patients where close follow up can be given
- Continue follow up and maintenance of vital functions.
  - Airway and ventilation
  - Controlling of blood pressure
  - Controlling body temperature
  - Fluid administration /Hydration
- If the patient is comatose or has impaired mental status
  - Changing the patients position every 2 hrs and avoid the occurrence of bed sores
  - Bladder and bowel care: if the patient has incontinence – catheterize
- Infections such as aspiration pneumonia should be treated with antibiotics

B. Management of Specific Etiologies

1) Atherosclerotic stroke (Thrombotic stroke)

i) Thrombolytic therapy: in developed countries thrombolytic therapy with medications such as rt-PA (plaminogen activator), to patients who present within 3 hrs of onset of stroke, helps to lyse the thrombus and restore perfusion to the affected brain.

Contraindications:

- Extensive infarct on CT,
- Recent surgery, Head trauma
- GI or urinary hemorrhage, bleeding disorders, Anticoagulation with prolonged PT/PT

- Seizure at stroke onset
- Severe uncontrolled hypertension.

ii) Anticoagulants: use of Heparin and Warfarin is controversial. Low dose heparin can be given for prevention of thromboembolism.

iii) Anti-platelet aggregation agents:

Aspirin reduces the incidence of stroke and vascular mortality. General recommendation is to give 325 mg of ASA once daily. It may not help to resolve the already formed thrombus, but ASA prevents recurrence of stroke.

2) Embolic stroke: (Cardiogenic embolus)

- Anticoagulation is indicated to prevent recurrent embolic stroke. Anticoagulation with heparin should be initiated when the acute phase of stroke is over. Care should be taken to avoid hemorrhagic transformation of infarct. Warfarin is used for chronic anticoagulation.

3) Intracerebral hemorrhage

- Continue supportive measures
- Control very high blood pressure
- Surgical consultation is indicated for removing cerebellar hematoma, as it may compress vital centers in the brainstem.

4) Subarachnoid Hemorrhage

Medical therapy:

(a)Supportive measures include bed rest, sedatives, analgesic, laxative,

(b)Control of hypertension and

(c) Nimodipin (calcium channel blocker) is given to prevent neurologic deterioration due to vasospasm.

Surgical therapy: Saccular aneurysms are treated surgically

C. Prevention of further stroke:

- Control of hypertension
- Control blood sugar in diabetics
- Ceasation of smoking
- Physical activity and weight reduction
- Anticoagulation for atrial fibrillation
- ASA 75 mg Po daily in individuals older than 50 and have history of TIA

- Surgery (Endarterioactomy): if a narrowed artery is detected

D. ***Rehabilitation:*** is a very important part of management, and it shall be started early and include:-

- Physiotherapy
- Occupational and speech therapy.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Cerebrovascular diseases, pages 2372-2392.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edtion Medicine, Stroke, pages 619-625.

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4. Impairment of consciousness and Coma

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define different levels of Impairment of consciousness and Coma.*
2. *List the etiologies of Impairment of consciousness and Coma.*
3. *Understand the diagnostic approach of Impairment of consciousness and Coma.*
4. *List differential diagnosis to Impairment of consciousness and Coma.*
5. *Understand the principles of management of patients with coma.*

Introduction

Maintenance of conscious state requires proper functioning of the cerebral hemispheres, reticular activating system found in brain stem and corticothalmic connections. If there is structural, metabolic or toxic insult of diffuse nature to these structures results in alteration of conscious level of different degree.

- ***Coma*** is severe degree of reduced consciousness (alertness and responsiveness) from which the patient cannot be aroused.
- ***Stupor*** is a sleep like unarousability, from which the patient can be awakened by vigorous stimuli.
- ***Drowsiness:*** is a state of reduced consciousness characterized by easy arousal that can be maintained only for brief period of time.
- ***Vegetative state:*** is characterized by the patient's unawareness of self or external stimuli. Autonomic functions are relatively well maintained, and a sleep-wake cycle exists. The patient cannot interact with others in a meaning full fashion. The patient can survive with medical and nursing support.
- ***Brain death:*** This is a state in which there has been cessation of cerebral blood flow; as a result there is global loss of brain function while respiration is maintained by artificial means and the heart continues to pump.

Etiologies

1. Diseases that cause no focal neurologic deficit or lateralizing neurologic signs. The loss of consciousness in such patients is diffuse bilateral hemispheric impairment, and such patients have normal brainstem function. Some of the causes include :-

- ***Metabolic disturbances such as :*** hepatic encephalopathy ,uremic encephalopathy ,hypoglycemia, diabetic ketoacidosis. Electrolyte imbalance (hyponatremia, hypernatremia, Hyperkalemia, Hypocalcaemia), Hypoxia, Hypercapnia etc
- ***Intoxications:*** alcohol, sedative drugs, opiates
- ***Sever systemic or CNS infections*** : meningitis, encephalitis, cerebral malaria, cerebral abscess
- ***Post seizure state*** : status epilepticus
- ***Hypertensive encephalopathy , eclampsia***
- ***Sever hyperthermia or hypothermia***
- ***Head trauma:*** brain concussion

2. ***Diseases that cause focal neurologic deficit:*** these disorders cause coma by affecting the reticular activating system. They are classified in to two depending on the location of the lesion.

a) Supratentorial (hemispheric) lesions

- Epidural or subdural hematoma
- Intraparenchymal hemorrhage (hemispherical hemorrhage)
- Large ischemic infarction
- Tumor , Abscess , Trauma

b) Infratentorial lesions

- Pontine or cerebellar hematoma
- Basilar artery thrombosis
- Ischemic cerebellar infarction
- Tumor , abscess

Approach to a patient in Coma

Complete and rapid assessment of the patient is critical for optimal care.

A. Assessment and maintenance of vital function is the initial step

- Maintain the air ways and ensure adequate breathing (ABC of life)
- Maintain circulation

B. Establishment of cause of coma*:* is done by taking a careful history, doing rapid but through physical examination and investigations.

Patient History:

Past medical history: looking for disease like diabetes, hypertension, cirrhosis, chronic renal disease, malignancies and other diseases.

- History of medications: legal or illicit drugs (sedatives, hypnotics, narcotics) and history of drug abuse
- Circumstances and rapidity with which change in mental status developed (sudden onset indicating vascular causes, gradual onset indicating metabolic and infectious causes fluctuations suggest subdural hematoma)
- Recent patient complaints preceding loss of consciousness: medical and neurologic symptoms (fever suggesting infections, polyuria and polydypsia indicating DKA)
- Details regarding the site where the patient was found (e.g. the presence of empty drug vials or evidence of fall or trauma

Physical examination should be through.

- ***Vital signs*****:** Extremes of BP, pulse or temperature and abnormal pattern of breathing.
  - Fever suggests systemic or CNS infections or Neurogenic fever
  - Tachypnea – in pulmonary infections or acidosis
  - Hypertension – hypertensive encephalopathy
- ***Head and neck***: evidence of trauma and the presence of meningismus
- ***Skin:*** look for signs of trauma or injection.
- **General systemic examination:** looking for evidences of systemic illnesses like cirrhosis, chronic renal, failure, meningococcemia etc.

Neurologic examination: is the cornerstone of assessment of comatose patient. It should be descriptive and systematic.

1. ***Level of consciousness:*** can be assessed semi quantitatively using the Glasgow coma Scale**.**

Table VIII-4-1 Glasgow coma Scale:

Eye opening	**Score**
Spontaneous	4
To verbal stimulus	3
To painful stimulus	2
None	1
Best verbal response	
Oriented	**5**
Confused	**4**

Inappropriate words	**3**
Unintelligible words	**2**
None	**1**
Best motor response	
Obeys commands	**6**
Localizes pain	**5**
Withdrawal from pain	**4**
Extensor response	**3**
Flexor response	**2**
None	**1**

Points are given for best response in each category and are added giving a score between 3 (deep coma) and 15(normal)

2. Brain stem reflexes

Assessment of brainstem functions helps to localize the cause of coma. This can be done using brain stem reflexes including, pupillary light response, ocular movements, corneal reflex and the respiratory pattern. If the brainstem functions are normal, coma must be ascribed to bilateral hemispherical disease.

a) Pupillary light response

Pupillary reactions are examined with a bright, diffuse light. During examination size, shape, symmetry and reaction to light should be noted on both eyes.

- Normally reactive and round pupils of midsize (2.5 to 5 mm) essentially exclude midbrain damage.
- Enlarged (>6mm) and unreactive pupil on one side signifies a compression or stretching of the third nerve from the effects of a mass above.
- Bilaterally dilated and unreactive pupils, indicates severe midbrain damage, usually from compression by a mass.
- Bilaterally small (1 to 2.5 mm) and reactive pupils (not pinpoint) are seen in metabolic encephalopathies or in deep bilateral hemispheral lesions such as hydrocephalus or thalamic hemorrhage.
- Very small but reactive pupils (< 1 mm)/pinpoint pupils, characterize narcotic or barbiturate overdoses but also occur with extensive pontine hemorrhage the thalamus.

b) Ocular Movements

Before maneuvers the eyes are observed by elevating the lids and noting the resting position and spontaneous movements of the eyeballs.

- Lid tone is tested by lifting the eyelids and noting their resistance to opening and the speed of closure. Resistance to opening the eye lids may suggest hysteric conversion. Easy eyelid opening with slow closure indicates sever coma.
- Midline deviation suggests frontal/pontine damage.
- Dysconjugate gaze (abduction or adduction) suggests cranial nerve abnormalities.
- Spontaneous eye movements roving, dipping, bobbing suggest damages being at different sites.
- The eyes look towards a hemispheric lesion and away from a brainstem lesion.

i. Occulocephalic reflex

Oculocephalic reflex is elicited by moving the head from side to side or vertically with eyes held open. In comatose patient with intact brainstem

- If the eyeballs move to the opposite direction of the head movement→intact brainstem function ("doll's eyes" movement is positive.)
- If the eyeballs move to the same direction of the head movement→ Brainstem dysfunction.

ii. Caloric (occulovestibular) reflex

- This test is performed by irrigating the ear with ice (cold) to stimulate the vestibular apparatus. In patients with intact brain stem the eyes move to the irrigated ear.

***c)* Corneal reflex**

- This test assesses the integrity of dorsal midbrain and pontine. It is lost if the reflex connections between the fifth (afferent) and the seventh (efferent) cranial nerves within the pons are damaged.

d) Respiration:

- Abnormalities of respiratory pattern can help in coma diagnosis but are of less localizing value in comparison to other brainstem signs.
  - ***Shallow, slow, but regular breathing*** suggests metabolic or drug depression.
  - ***Cheyne-Stokes respiration*** signifies bihemispherical damage or metabolic suppression, and commonly accompanies light coma.

- ***Rapid, deep (Kussmaul) breathing*** usually implies metabolic acidosis but may also occur with pontomesenephalic lesions and severe pneumonia.
- ***Agonal gasps*** reflect bilateral lower brainstem damage and are indicators of severe brain damage and a near death situation.

3. Motor function /response

Posture of the patient:

- ***Quadriparesis and flaccidity***: suggest pontine or medullary damage
- ***Decorticate posturing:*** flexion of the elbows and the wrists with supination of the arms, and extension of the legs, suggests severe bilateral or unilateral hemispheric or diencephalic lesion (damage above the midbrain.)
- ***Decerebrate posturing*** (extension of elbows and the wrist with pronation of the forearm and extension of the legs) indicates damage to the brainstem(midbrain or pontine compromise)
- ***Spontaneous activities*** – if the patient is yawning, swallowing, coughing or moaning the coma is not deep.
- ***Abnormal body movements*** – seizure, myoclonus may suggest the cause of the coma is status epelepticus, uremia etc.
- Assess tone, response to painful stimuli and presence of asterixes. Asymmetric motor responses have localizing value.

Differential Diagnosis:

Psychogenic Coma (hysteric coma): patient often has history of psychiatric illness, and non physiologic response on physical examination.

- Resistance to having the eyelids opened (the patient resists eyelid opening when the examiner tries to open it)
- Failure of the patient's arm, when held by the examiner over the patent's face, to fall up on the face when released by the examiner.
- Nystagmus when the ear is irrigated with cold water
- Adversive head and eye movements

Laboratory investigations

- ***Blood film, CBC, urine analysis***
- ***Measurements of serum glucose level, renal and liver function test.***

- ***Lumbar puncture and CSF examination*** should be done as soon as possible unless increased intracranial pressure is suspected to exclude infections and subarachnoid hemorrhage.
- Measurements of serum electrolytes, cultures, toxicological analysis, arterial blood gas analysis, EEG and imaging studies are also helpful in diagnosis of coma if available.

Management

Ideally the, care of comatose patient is started together with the initial assessment to identify the etiology.

a) ***Initial therapy*** : Maintaining an adequate airway, optimal ventilation and maintaining adequate perfusion (blood pressure)

- o If there is possibility of cervical fracture, immobilization of the neck is essential
- o Endothracheal intubation is often indicated to protect the airways
- o Blood samples for CBC, electrolyte glucose, RFT, LFT etc should be obtained.
- o Intravenous thiamine: 100 mg IV with 50 % glucose solution is given. This treatment is given if hypoglycemia is even remote possibility, and thiamine is given with glucose in order to avoid eliciting Wernicke disease in malnourished
- o Naloxone(0.4mg) is administered in case of opiate intoxication
- o Flumazenil can be given if benzodiazepine or hepatic coma is suspected
- o Correct any associated problem like hypertension, hypoglycemia hyperthermia and hypoxia

b) ***Give care of comatose patient:***

- Monitor vital signs
- Provide adequate ventilation and oxygenation.
- Maintain appropriate position and change position frequently
- Catheterize and insert nasogastric tube

c) Manage the primary cause of coma.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Acute confusional state and Coma, pages 1624-1630.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edtion Medicine, Loss of consciousness, pages 600-605.

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5. Seizure and Epilepsy

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define Seizure and epilepsy.*
2. *Describe the international classification of Seizure.*
3. *Understand the epidemiology of Seizure and epilepsy.*
4. *List the etiologies or risk factors for Seizure disorder.*
5. *Identify the clinical manifestation of different types of Seizure disorders.*
6. *Understand the Evaluation and diagnostic approach to Seizure.*
7. *Identify complications of Seizure.*
8. *List differential diagnosis for Seizure.*
9. *Manage patients with Seizure or epilepsy.*
10. *Understand status epileptics and its management.*

Definition: *Seizure* is a paroxysmal event due to abnormal excessive discharge of cerebral neurons. The paroxysmal event may be subtle or dramatic. Depending on the distribution of the discharge, the manifestations may be:

- Motor
- Sensory
- Autonomic or
- Psychiatric manifestation.

Epilepsy – is a syndrome characterized by recurrent (two or more) unprovoked seizure attacks, due to a chronic, underlying process in the brain. This definition implies that a person with a single seizure, or recurrent seizures due to correctable or avoidable circumstances, does not necessarily have epilepsy.

International classification of seizures:

Epileptic seizures can be classified in many different ways. Commonly used classification is the one developed by International League against Epilepsy.

1) Partial seizures: beginning locally

a) Simple partial seizure: (with motor, somatosensory, autonomic or psychiatric symptoms
b) Complex partial seizure
c) Partial seizures with secondarily generalization

2) Generalized seizures

a) Absence seizures (petit mal)
b) Tonic – clinical seizures (grand mal)
c) Myoclonic seizures
d) Clonic seizures
e) Tonic Seizures
f) Atonic seizures

3) Unclassified

a) Neonatal seizures
b) Infantile spasm

The basis for this classification is manifestations during seizure attack and EEG feature between attacks. This classification is useful in understanding underlying etiology, selecting appropriate treatment and understanding the prognosis of seizure type.

Epidemiology

- Epilepsy is estimated to affect 0.5-4% of the population around the world.
- The prevalence is said to be higher in developing countries.
- Grand mal seizure account for 40 to 80 %of all types of epileptic seizures.
- It is estimated that 5-10 % of the population will have at least one seizure attack in their life time, with the highest incidence occurring in early childhood and late adulthood.
- In Ethiopia based on a study done by Teklehaymanot R. the prevalence of active epilepsy is estimated to be 5.2/1000. Analysis of 468 epileptics seen in neurology clinics of Addis Ababa showed highest incidence in males aged 11-20 years. The commonest type of seizure was found to be grand mal seizure accounting for 60% of all cases.

Etiology of seizure or risk factors:

The causes of epilepsy/seizure are vary greatly in different age groups and across different regions of the world

- ***Idiopathic or cryptogenic*:** in which the cause is unknown, accounts for the majority.
- ***Genetic factor*** (Family History)
- ***Perinatal causes***: perinatal asphyxia, birth trauma, perinatal infection
- ***CNS infections***: encephalitis, toxoplasmosis, cerebral malaria,

- ***Head trauma:*** penetrating head injury, depressed skull fracture, intracranial hemorrhage and prolonged post traumatic coma are associated with increased risk of having seizure disorder.
- ***Neoplasms***: metastatic or primary brain tumors
- ***Vascular causes***: Infarction or stroke, vascular malformations
- ***Metabolic abnormalities***: hyponatremia, hypo or hyperglycemia, Uremia
- ***Inflammatory causes***: Systemic lupus erythromatus
- ***Degenerative diseases:*** Alzheimer's disease
- ***Drugs:*** Thephylline, Cocaine, Lidocaine

Clinical features

I. Partial Seizures: these are seizures, which arise from localized region of the brain.

a) Simple partial/focal seizures

- These are seizure activities in which consciousness is not impaired.
- Manifestation can be motor, sensory, autonomic or psychiatric.
- Motor manifestation is usually focal clonic or tonic movement of angle of mouth, finger or thumbs. This seizure activity may spread over one side of the body (Jacksonian march) to involve larger body part. (E.g. the convulsive activity can start in the face, move to ipsilateral arm, and then to the leg)
- The rest of manifestations include transient sensory abnormalities, flushing and sweating or odd feelings.

b) Complex partial seizure

- These are focal seizures activities accompanied by impairment of the patient's ability to maintain normal contact with the environment. The patient is unable to respond appropriately to visual or verbal commands during the seizure, and has impaired recollection or awareness of ictal phase.
- The seizure frequently begins with an aura , which may manifest with hallucination (e.g. Olfactory . visual , auditory or gustatory) and complex illusions (e.g. having experienced a new event)
- The start of the ictal phase is often a sudden behavioral arrest or motionless stare, which is often accompanied by automatism, which is involuntary automatic behavior (repeated complex activities like chewing, lip smoking, "picking movement" of the hands , and display of emotions).

- They have also post-ictal confusion and transition to full recovery may take minutes to hours.

c) Partial seizure with secondary generalization

- These are focal seizures, which evolve into a generalized seizure. These are usually tonic-clonic type and difficult to differentiate from primary generalized tonic-clonic seizure.

II. Generalized seizures

There are seizure disorders which arise from both cerebral hemispheres simultaneously, with without any detectable focal onset.

a) ***Absence seizure*** :

- It is characterized by sudden and brief lapses of consciousness without loss of postural control.
- The seizure typically lasts for only few seconds, consciousness returns as sudden as it was lost.
- It usually manifests with blank staring and they may have also subtle motor manifestations like blinking of the eyes, chewing movements.
- There is no post-ictal confusion.
- The seizure may occur as many as hundreds of times per day
- It is usually detected by unexplained daydreaming and decline in school performance.
- It usually begins in childhood (4- 8 yrs) , and it often has a good prognosis, with 60-70 5 of such patients will have spontaneous remission during adolescence.

b) **Generalized tonic clonic seizure (Grand mal)**

- Is the most common seizure type.
- The seizure usually begins abruptly without warning (no aura or focal manifestations.)
- ***The ictal phase*** is begins with tonic contraction of muscles throughout the body , which is responsible for loud moan or cry (due tonic contraction of the muscles of respiration and the larynx), tonic posturing, respiration is impaired and the patient falls to the ground, and there may be tongue biting due to tonic contraction of the jaw muscles. After 10 – 20 seconds the tonic phase evolves to clonic phase characterized by bilateral jerking clonic movement involving the whole body. This lasts for another 1 minute.

- ***The post-ictal phase*** is characterized by unresponsiveness, muscle flaccidity, excessive salivation and frothing of saliva which may cause stridorous breathing and partial airway obstruction. Bladder or bowel incontinence may occur at this point. Patients gradually regain consciousness over minutes to hours, and during this transition there is typically a period of postictal confusion, headache, muscle ache and fatigue that can last for many hours.

c) Atonic Seizures:

- Are characterized by sudden loss of postural muscle tone, lasting 1 to 2 seconds.
- Consciousness is briefly impaired.
- It usually manifest as a head drop or nodding movement, while a longer seizure may cause the patient to collapse

d) Myoclonic seizure :

- Is characterized by a sudden and brief muscle contraction that may involve one part of the body or the entire body.
- A normal common physiologic form of myoclonus is sudden jerking movement observed while falling asleep.
- Pathologic myoclonus is most commonly seen with metabolic disorders, degenerative diseases of the CNS or anoxic brain injury .

Complications

- Status epilepticus
- Accidents
- Hypoxic brain damage
- Mental retardation and impairment of intellectual function
- Sudden death
- Psychosocial (Social stigma).

Diagnostic approach/Evaluation

Patient's history and physical examination can aid in the determination of whether or not a seizure or some other transient event was responsible for the patient's symptoms

History should include: -

History of the event

- Presence of any prodromal symptoms
- Description of seizure by reliable observer

- Post ictal symptoms
- Urinary incontinence, myalgia and tongue bite or oral lacerations are clues to the proper diagnosis.

History of suggesting cause and risk factors

- Febrile convulsion (history of high grade fever)
- CNS infections (current /Previous)
- Head injury
- Stroke
- Developmental abnormality
- Family history
- Social history (like alcohol abuse)

Physical examination: features that should be looked for include

- Skin for evidence of Neurofibromatosis
- Organomegaly: Metabolic storage diseases
- CVS/ carotid artery - stroke
- Complete neurological exam.

Investigations

- ***EEG (Electroencephalography)*** is most useful test in diagnosis of seizure disorder. It should be performed while the patient is asleep and awake. Abnormal EEG supports the diagnosis of seizure and may give information about the type of seizure. However abnormal EEG is not adequate for diagnosis of seizure and normal EEG can be found in epileptics.
- ***Neuroimaging preferably MRI*** : may help to see any space occupying lesion in the brain
- ***Other routine laboratory assessment*** may be required in management of patients with epilepsy (CBC. Urinalysis, serum glucose, liver function test, renal function test electrolytes, toxicological screening).

Differential Diagnosis for Seizure

- Syncope
- Psychogenic seizure (hysteric conversion)
- Transient Ischemic attack
- Migraine

Management:

Goal of therapy:

- Complete control of seizure
- Prevent development of complications and socioeconomic consequences.

Treatment of seizure includes:-

1. Treatment of underlying condition

- Metabolic disorders such as hypoglycemia, hyponatremia or drug intoxication should be corrected
- Structural CNS lesion lie tumors may be removed surgically.

2. Avoidance of precipitating factor

- Maintain normal sleep schedule
- Avoid taking excess alcohol
- Reduce stresses using , physical Exercise , meditation or counseling

3. Suppression or control of recurrent seizure

Antiepileptic drug therapy (AEDT)

- The Goal of antiepileptic therapy is to achieve complete control of seizure with no or minimal side effects, preferably using single agent and easy dosing schedule

When do we start anti epileptic drugs?

- ***Recurrent seizure of unknown cause or a known cause that cannot be reversed***
- ***Single seizure due to*** :
  - Identified CNS lesion (tumor, infection, trauma)
  - With abnormal neurologic exam
  - Presenting as status epilepticus
  - With post-ictal Todd's paralysis
  - With strong family history of seizure disorder
  - With abnormal EEG

- ***Note:*** anticonvulsant therapy is not often initiated in patients with a single, unprovoked convulsion, a normal neurologic examination, and a normal neuroimaging study and EEG unless they experience a second seizure.

General principles:

- An attempt is usually made to prevent subsequent seizure using a single agent , in order to limit side effects.
- The drugs should be administered in progressive dose until seizure control has been achieved or until drug toxicity occurs.
- Only if monotherpay fails should a second drug be added to the patient's regimen. If control is achieved, then the first agent might be carefully withdrawn.
- A number of drugs are available for treatment of epilepsy and the choice of medication is based on the seizure type

Table VIII-5-1 Selection of antiepileptic drugs

	Primary GTCS	Partial	Absence	Atypical absence , myoclonic, Atonic
First line	Valproic acid Lamotrigine	Carbamazepine Phenytoin Valproic acid	Valproic acid Ethusuximide	Valproic acid
Second line	Phenytoin Carbamazepine Phenobarbitone	Topiramate Phenobarbitone	Lamotrigin Clonazepam	Lamotrigin Clonazepam Topiramate

i. Phenobarbitone

- In developing countries, Phenobarbitone is the drug of choice for the control of partial and GTC seizures, due to the wide availability and cheaper cost of the drug.
- Its efficacy is quite acceptable in comparison to most of the AEDS, but it has some side effects that might interfere with compliance. These side effects have to be explained to the patient and his family early on.
- This drug is available in the following dosage forms: 15, 30, 60 and 100 mg tablets.

Dosage:

- The usual starting dose for adults is 60 PO daily. If seizure is not controlled the dosage may be increased gradually at intervals of no less than 2-3 weeks to a maximum dose of 200 mg PO BID.

Common side effects of Phenobarbitone

- Fatigue , Listlessness , depression
- Insomnia (especially in children)
- Distractibility and short attention span (especially in children) and Hyperkinesia , Irritability
- Poor memory
- Decreased libido

In cases of treatment failure or poor control with maximum tolerable doses of drug, a second AEDS is often added to the regimen. The addition of a second drug is associated with worsening of adverse effects; hence care should be taken, before one decides to add a second drug to the original regimen.

ii. ***Phenytoin:*** is the usual prescribed as a second line drug in resource limited settings like ours mainly because of its availability and cost.

Dosage:

- 100 mg PO BID or TID , which may be gradually increased to a maximum of 200 mg PO TID (i.e. 600 mg daily)

Side effects:

- CNS : nystagmus , ataxia
- Gingival hyperplasia
- Coarsening of facial feature
- Toxic hepatitis and liver damage

iii. ***Carbamazepine***: is also available in Ethiopia. It is often given for the treatment of partial seizure

Dosage: a low initial dosage with gradual increase is advised.

- 200 mg Po BID and gradually increase the dosage by 2OO mg every week until the best response is achieved or maximum dose of 1600 mg daily.

Side effects

- Aplastic anemia
- Dizziness drowsiness

- Skin rash
- Transient diplopia

When to stop antiepileptic drugs?

- It is common practice to continue treatment until the patient has been seizure free for at least 3 years.
- Thereafter, consideration of drug withdrawal is based on a number of factors like:-
    - The ease with which control was achieved starting from the time of AED drug initiation.
    - The type of seizure
    - The presence of other neurological co-morbidity e.g. mental retardation, focal neurological deficit.
- The probability of relapse after stopping treatment is somewhere around 10-40%
- It is not known whether remissions for 3 or more years consist of "cure" or " control" and so drug withdrawals have to be gradual, over a period of months to minimize the risks of relapse.
- Most relapses occur within a year of discontinuing of medications. The more severe and long lasting a patient's active epilepsy before remission, the greater the risk of relapse.

When to refer patients to a neurologist or tertiary level hospital

- Failure to respond to treatment
- Recurrence of previously controlled seizure
- Change in clinical pattern of seizure
- Appearance of previously absent symptoms/sign
- Development of side effects of a drug

4. Managing psychosocial issues

- ***Social stigma*** : avoid misconceptions in the public through health education
- ***Psychiatric problems*** : depression , psychosis ,anxiety should be treated
- ***Social problems*** (education, employment, marriage): encourage patients to go school /work to get married and establish family.
- ***Educate Patients and families:*** about the diseases and what precautions patient should take.
    - Seizure /epilepsy can be controlled by drugs
    - Drug discontinuation creates problem and follow up is important
    - ***Advice Patients to avoid***

- Alcohol/ other drugs or substances like “Chat”
- Heights
- Cooking with open fire
- Machineries that may cause injury
- Swimming
- Driving

▪ ***What should families or attendants do during active seizure***

- No traditional treatment is beneficial
- To be calm
- Loosen patient’s clothing
- Keep from injury
- Turn head to side
- Do not insert anything into the month

Surgical Therapy: Patient’s refractory to medical control of seizure may benefit from surgery to control the epilepsy. Surgical interventions include

- Temporal lobe resection
- Corpus callosum sectioning

Status epilepticus

- A condition characterized by continuous or repetitive discrete seizure with impairment of consciousness during interictal period, which lasts for more than 30 minutes. It is a medical emergency

It can be caused or precipitated by

- Non compliance with AED
- CNS infections
- Metabolic derangement
- Tumors
- Trauma
- Stroke
- Refractory epilepsy

Clinical features:

Generalized status epilepticus is obvious when the patient is having over convulsion, however after 30-35 min of uninterrupted seizure, the signs may become increasingly subtle. Patients may have mild clonic movement of only the fingers, or fine, rapid movement of the eyes.

Complications of Status epilepticus:

- Aspiration
- Hypoxia
- Metabolic acidosis
- Hypotension
- Hyperthermia
- Rhabdomyolysis and associated myoglobinuria
- Multiple physical injures including vertebral bone fracture
- Irreversible neuronal injury

Management

1. ***Emergency supportive measures***

   Keep Airway patent and maintain breathing

   Secure IV line and take blood for laboratory investigation

   Give glucose IV with Thiamine

2. ***Control the seizure*** with anticonvulsant

   1st step: Lorazepam 0.1 mg/kg IC at a rate of 2mg/min or Give diazepam IV 5- 10 mg IV

   2nd step: Phenytoin 20 mg/kg IV at a rate of 50 mg /min if seizure continues

   3rd step: Phenobarbital 20 mg/kg IV at a rate of 50 -75 mg/min, if seizure still continues

   4th Step: General anesthesia with Medazolam, Propofol or pentobarbitol, if seizure becomes refractory

In resource limited setting Diazepam 5-10 mg IV is given 2-3 times, and if the seizure is not controlled Phenytion 1000 mg PO is given through NG tube. Phenobarbitone can also be used.

3. ***Treat the precipitating cause (metabolic abnormalities or infections)***
4. ***Give maintenance antiepileptic drug:*** after the acute condition is controlled.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Seizure and Epilepsy, pages 2357-2371.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Seizure, pages 626-628.

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6. Parkinson's Diseases and other movement disorders

Learning objectives: at the end of this lesson the student will be able to**:**

1. *Define Parkinsonism and Parkinson's disease.*
2. *List the etiologies or Parkinsonism.*
3. *Understand the epidemiology and risk factors for Parkinsonism.*
4. *Describe the clinical manifestation of Parkinson's diseases.*
5. *Understand the principles of management of Parkinson's diseases.*
6. *Understand the basic clinical features of other movement disorders.*

Parkinsonism:

***Definition*:** Parkinsonism is a clinical syndrome characterized by**:-**

- ***Bradykineisa***: slowness and paucity of movement
- ***Tremor:*** This occurs at rest
- ***Rigidity***
- ***Snuffling gate*** and
- ***Flexed posture***

Etiologies:

1. **Parkinson's Diseases:** It is sporadic and idiopathic with unknown etiology.
   - Is the commonest cause of Parkinsonism accounting for 75 % of all cases?
   - It is characterized by degeneration of cells in the ***substantia nigra,*** which causes deficiency of dopamine (a neurotransmitter) in the CNS, leading to a series of changes in motor control pathways. These degenerative changes are believed to be due to accumulation of the presynaptic protein α-synuclien.
2. ***Other known causes*** **:** *account for 25 % of all cases*

a) ***Familial (primary Parkinson's diseases)***

b) ***Other neurodegenerative diseases***

- Shy-Drager syndrome
- Motor neuron disease with PD features
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Wilson's disease

- Huntington's diseases

c) ***Miscellaneous acquired conditions***

- Vascular parkinsonism (stroke affecting the extrapyramidal structures)
- Normal pressure hydrocephalus
- Cerebral palsy
- Repeated trauma:" dementia puglistica" with parkisonian features (e.g. seen in professional boxers like Mohamed Ali)
- Infectious : post encephalitis PD , Neurosyphilis
- Hypothyroidism or pseydohypoparathyriodism
- Drugs:
- Neroleptics (antipsychotics e.g. Haloperidol ,Chlorpromazine
    - Antiemetics : metoclopromide ,
    - Methyldopa
    - Valproic acid
- Toxins : Cyanide , Methanol , Carbon monoxide, manganese

Epidemiology:

- PD affect > 1 million people in US (1 % of those > 55 years)
- The peak age of onset is the 60s (range is 35-85 years)
- Familial PD tend to have an earlier age of onset (typically before the age of 50 year)

Risk factors for Parkinsonism include

- *Positive family history*
- *Male gender,*
- *Head injury*
- *Exposure to pesticides*
- *Consumption of well water*
- *Rural living*

Clinical Features

A diagnosis of PD can be made with some confidence in patients with some confidence in patients who present with at least 2 of the three cardinal signs –rest tremor, rigidity and bradykinesia

Motor Features

Resting tremor:

- It is present in 85 % of patients with true PD, and a diagnosis of PD is difficult when tremor is absent.
- It starts unilaterally and has a gradual onset, affecting first distally involving the digits and wrist where it may present with "pill –rolling" character.
- Tremor usually spreads proximally, ipsilaterally and occasionally to the leg, before crossing to other side after a year or two.
- It may appear later in the lips, tongue, and jaw but spears the head.

Bradykinesia/akinesia:

- It is the most disabling feature which interferes with all aspects of daily living. Patients have trouble in walking, rising from seated position, turning over in bed, dressing etc.
- Fine motor movement is also impaired as evidenced by decreased manual dexterity and hand writing (micrographia)
- Soft speech (hypophonia) is the other of bradykinesia.
- Masked face , decreased eye blinking

Rigidity:

- Is felt as a uniform resistance to a passive movement about a joint throughout the full range of motion. Brief regular interruption of resistance during passive movement may give rise to"cogwheels rigidity.

Gait disturbance:

- Patients have shuffling short steps, and a tendency to turn en bolc ,
- ***Festinating gait,*** a typical feature of Parkinsonism, result from a combination of flexed posture and loss of postural reflux, which causes the patient to accelerate in an effort to catch up with the body's centre of gravity.
- ***Freezing of gait***: is a feature of more advanced PD, occurs commonly at the onset of locomotion (start hesitation), when attempting to change direction to turn around and upon entering narrow space such as a doorway.
- Abnormalities of balance and posturing: tends to increase as the disease progress
- ***Stooped posture***: flexion of the head, stooping and tilting of the upper trunk, and tendency to hold the arm in flexed posture while waking is common.
- In advanced diseases postural instability may lead to frequent falls and injuries.

Non motor features:

- ***Loss of sense of smell*** (anosmia)
- ***Sensory abnormalities*** often manifest as distressing sensation of inner restlessness and aching pain in the muscles of the extremities which often develops as anti Parkinson's medications are wearing off.
- ***Sleep disorders*** are common in PD, which may manifest as day time drowsiness frequent napping. This may result from disrupted sleep from night time worsening of symptoms and difficulty of turning over in bed
- **Autonomic dysfunction:** may manifest with orthostatic hypotension, constipation urinary urgency and frequency , excessive sweating

Neuropsychiatric System

- ***Depression*** affects approximately half of patents
- ***Anxiety*** **disorders**
- ***Cognitive abnormalities***: affect many patients and it may manifest with difficulty of doing complex tasks, long term planning, and memorizing or retrieving new information. Dementia is 6X more common in PD patients than their age matched controls.
- ***Psychotic symptoms***: affect 6 – 40 % of patients with PD, visual hallucination are common symptoms, and depression and dementia are risk factors for developing psychiatric symptoms.

Treatment

- The goal of therapy in PD is to maintain function and quality of life and to avoid drug induced complications
- Parkinson's disease is a progressive disease, therefore management protocols vary depending on the patient symptoms and the extent of functional impairment.

1. Pharmacotherapy of motor symptoms:

- Therapy to control motor symptoms should be initiated as soon as the patient's symptoms begin to interfere with the quality of life.

Early Parkinson's disease:

a) ***Selegilline*** is selective and irreversible mono aminoxide (MAO) inhibitor.

- It may slow the clinical progression of Parkinson's diseases and delay the need for other medication. This drug has minimal effect on symptoms when used as monotherapy or as an adjuvant to Carbidopa/levodopa.

- Selegilline is used as an initial therapy or added to alleviate tremor of Carbidopa/levodopa associated wearing effect

Dose: 5 mg PO with breakfast and lunch

b) ***Dopamine agonists***: have direct post synaptic effect on do dopamine receptors.

- Dopamine agonist monotherpay is well tolerated and significantly reduced the risk of later treatment –related complications such as motor fluctuation and dyskinesia associated with Carbidopa/levodopa treatment.

Non Ergot alkaloids:

- ***Rupinirole:*** Initial dose 0.25 mg Po TID to maximum target dose as monotherapy is 12-24 mg/day
- ***Parmipexole*** ; Initial dose 0.125 mg PO TID maximum target dose as monotherapy is 1.5-4.5 mg /day

Ergot alkaloids

- ***Pergolide***; Initial dose 0.05 mg PO TID to maximum dose 1.5-6 mg /day
- ***Bromocriptine***: Initial dose 1.25 mg Po BID or TID, to maximum target dose as monotherapy 7.5-15 mg/day

- When dopamine agonists are used as monotherapy, higher doses are required to control symptom. However the dose should be titrated gradually.
- Most patients require the addition of levodopa or another agent, within 1-3 yrs of initiating dopamine agonists
- Older patients and those with akinetic rigidity have a low risk of motor complications and dyskinesia, and may be satisfactorily treated with levodopa as an initial therapy.

Advanced Therapy

c) ***Levodopa/Carbidopa Formulation (Sinemet®, Atamet®)***

- ***Levodopa***: is converted to dopamine by presynaptic neuron and therefore increase the amount of neurotransmitter available to the post synaptic dopamine receptor.
- ***Carbidopa:*** blocks systemic/peripheral conversion of levodopa to dopamine, thereby decreasing the undesirable systemic effects of levodopa such as nausea and orthostatic hypotension.

Dose:

- ***Carbidopa/levodopa*** IR 25/100 mg Initial dose: t/2 tab PO TID, to maximum target dose of 3-6 25/100 mg tabs /day (i.e. 1 -2 tabs PO TID)
- ***Carbidopa/levodopa*** CR 50/200 mg tabs : dose 1tab BID or TID

The dosage of these drags should be escalated gradually

Wearing- off effects: management of Parkinson's disease becomes increasingly difficult as the disease progresses. Late treatment related complications include.

- ***Dsykineisa:*** refers to choreiform and dytonic movements that occur as a peak dose effect or at the beginning or end of the dose.
- ***Motor fluctuation:*** (on and off phenomenon) these are wide random swings in the patient's mobility or exaggerated ebb and flow of Parkinsonian signs, experienced by many patients between doses of anti-Parkinson medication.

More than 50 % of patients with PD treated over five years with levodopa will develop these complications

d) ***Levodopa Augmentation :***

i) Catechol O-methytransferase (COMT) inhibitors

- Estacapone and tolcapone offer augmentation of the effect of levodopa by blocking enzymatic degradation of levodopa and dopamine.
- These drugs are used in conjunction with Carbidopa/levodopa , they alleviate the wearing off symptoms

ii) Anti-cholinergics :are given as adjuncts to dopaminomimetic therapy

- They are useful in controlling resting tremor and dystonia
- Bezhexol is a drug which is available and commonly used

iii) Amantadine : has anti-cholinergic and dopaminomimetic properties

- It helps to reduce drug induced dyskinesia
- Can be effective early in the course of the diseases, or as an adjunct therapy later in the diseases course to help " smooth out " motor function

2. Neuroprotective therapy

Reducing the progression of PD through neuroprotective or restorative therapy is a major focus of research. Some of the neuroprotecitve treatment trails arte

- ***Non steroidal anti-inflammatory agents***
- ***Estrogens replacement therapy*** in post menopausal women
- ***Selegilline therap***y delays the need for levodopa therapy by 9 -12 months in newly diagnosed patients. Studies demonstrated that patients who remain on Selegilline for 7 yrs experienced slower motor decline.

3. Therapy of non motor symptoms

- ***Insomnia due to nocturnal akinesia*** : treated with night time supplemental dose of Carbidopa /levodopa
- ***Depression :*** Responds to anti depressants like Amitriptyline
- **Psychotic patients**: first remove anticholinergics and amantadine if the patient is taking. Reduce the dose of dopaminomimetic if the patient is not responding. If still the patient has psychotic symptoms and signs, start antipsychotics with minimal extrapyramidal side effects.
- ***Dietary manipulation*** : limiting protein intake during the day may improve levodopa's efficacy
- ***Physical therapy*** and an exercise program help to optimize mobility.

Surgical therapy

- ***Pallidotomy , and thelamothomy*** ; may be a therapeutic option for refractory Parkinson's diseases
- ***Neurotransplantation***: Transplantation of fetal substantia nigra tissue or cells.

Other movement disorders

Hyperkinetic disorders: these are disorders associated with increased movement.

1. Tremor

a) Benign essential tremor is characterized by posture related 5-9 Hz oscillation of hands and forearms that impairs performance of fine motor tasks.
   - This type of tremor is familial and may be accompanied by titubation (head tremor/bobbing)
   - Consumption of alcohol may temporarily suppress the tremor: stress , caffeine or sleep deprivation may exacerbation the condition
   - β-adrenergic blocking agents are effective in controlling tremor.

a) An Action (kinetic) tremor is evident when the patient moves his or her arms; there may be a relatively mild accompanying postural and intention component.
   - Clonazepam treatment can be useful.

2. Myoclonus

Definition: a brief, lightning-like contraction of a muscle or group of muscles.

Etiology:

- Metabolic derangements (e.g. uremia)
- Degenerative diseases (e.g. Alzheimer's)
- Slow virus infections (Creuzfeldt-Jakob disease, subactue sclerosing panencephalitis)
- Severe closed head trauma
- Hypoxic-ischemic brain injury

Signs and symptoms:

- Myoclonus may occur normally as a person falls asleep (nocturnal myoclonus).
- Common hiccup (singultus) is a form of myoclonus affecting the diaphragmatic muscles.
- Action myoclonus: is a myoclonus that increases with intended movements, It occurs typically after brain injury;
- Palatal myoclonus is a continuous, rhythmic contraction of posterior pharyngeal muscles.

Treatment:

- Correct underlying metabolic abnormalities.
- Clonazepam 0.5-2 mg PO. TID or valproate may be effective.

3. *Tics*

- Brief, rapid, simple or complex involuntary movements, which are stereotypical and repetitive, but not rhythmic.
- ***Simple motor tics*** (e.g. blinking) often begin as nervous mannerisms in childhood or later, and disappear spontaneously.
- ***Complex motor tics*** often resemble fragments of normal behaviour such as touching, smelling and jumping.
- ***Simple phonic tics*** include throat clearing, sniffing and grunting and complex phonic tics include the repetition of words and coprolalia.
- ***Tourette's syndrome***: a complex type of tics disorder characterized by multiple motor and one or more phonic tics that may occur many times a day, nearly every day for more than 1 year.

Treatment

- Education of patients and their family
- Drugs: Clonidine, Haloperidol

3. Chorea and Athetosis

Definition:

- ***Chorea:*** is brief, purposeless involuntary movements of the distal extremities and face, which may merge imperceptibly into purposeful or semi purposeful acts that mask the involuntary motion.
- ***Athetosis:*** is writhing movements, often with alternating postures of the proximal limbs that blend continuously into a flowing stream of movement. Both often occur together (choreoathetosis).

Etiology:

- Huntington's disease (see below)
- Thyrotoxicosis
- SLE
- Drugs (antipsychotics)

4. Chorea gravidarum

- It is choreiform movement occurring during pregnancy, often in patients with a history of rheumatic fever.
- Chorea usually begins during the first trimester and resolves spontaneously by or after delivery. Rarely, a similar disorder occurs in women taking oral contraceptives.
- Treatment consists of sedation with barbiturates, because other drugs may harm the fetus.

5. Hemiballismus

- It is violent, continuous proximal limb flinging movements confined to one side of the body, usually affecting the arm more than the leg.
- It is caused by a lesion, usually an infarct, in the region of the contralateral sub-thalamic nucleus of Luys.
- Differential diagnosis includes acute hemichorea, usually due to tumor or infarct of the caudate nucleus, and focal seizures. Although disabling, hemiballismus is usually self-limited, lasting 6 to 8 wk.
- Treatment with antipsychotics is often effective.

6. Huntington's Disease

Definition: also called Huntington's chorea, chronic progressive chorea or hereditary chorea. It is an *autosomal dominant disorder characterized by choreiform movements and progressive intellectual deterioration, usually beginning in middle age.*

Etiology: *Genetically determined.*

Signs and symptoms: *Develop insidiously.*

- *Dementia or psychiatric disturbances may precede the disease or develop during the course (anhedonia, asocial behaviour).*
- *Motor manifestations:* flicking movements of the extremities, a lilting gait, motor impersistence (inability to sustain a motor act, such as tongue protrusion), facial grimacing, ataxia, and dystonia. Disorder is always progressive; patients ultimately lose physical and mental abilities to care for themselves.

Treatment:

- No treatment for the underlying cause.
- Antipsychotics may control behaviour problems (e.g. chlorpromazine 100-900 mg/d PO or haloperidol 10-90 mg/d PO).

7. Dystonia

Definition: Sustained abnormal posture and disruptions of ongoing movement, resulting from alterations in muscle tone; it is classified as generalized, focal or segmental:

Generalized dystonia (dystonia musculorum deformans)

- It is a rare progressive syndrome characterized by movements that result in sustained, often bizarre postures.
- Symptoms usually begin in childhood with inversion and plantar fixation of the foot while walking.
- Generalized dystonia is often hereditary.
- In its most severe form, the disorder can be relentlessly progressive. Severely affected patients may become twisted into grotesque fixed postures.
- Mental function is usually preserved.

Focal dystonia affects a single body region. Rarely, dystonic movements spread to an adjacent region **(segmental dystonia),** and even more rarely, the process generalizes.

Treatment:

Treatment is often unsatisfactory.

- For **generalized dystonia,** high-dose anticholinergics and/or the dopamine-depleting drug reserpine 0.1-0.6 mg/d PO are most often used. Levodopa and carbamazepine benefit a few patients.
- For **focal or segmental dystonias** or for generalized dystonia that severely affects specific body regions, local injection of purified botulinum a toxin is the treatment of choice.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Parkinson's diseases and other movement disorders, pages 2406-2417.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edtion Medicine, Movement disorders, pages 629-633.

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7. Peripheral neuropathy

Definition: A general term indicating peripheral nerve disorder of any cause.

Classification of neuropathies

Neuropathies may be classified based on:

1. ***The type of symptoms and signs*** *: Sensory , Motor , Autonomic , Or any combination*
2. ***Distribution***
   - ***Mononeuropathy:*** single nerve affected
   - ***Multiple mononeuropathy(mononeuritis multiplex)*****:** two or more nerves in separate areas affected
   - ***Polyneuropathy:*** many nerves simultaneously affected
3. ***Course*** *:* (acute , subacute or chronic)
4. ***Nerve conduction test (NCT):*** Axonal or Myelin sheath

Etiology:

Table VIII-7-1 Etiologies of neuropathies based the predominant symptoms or signs

	Causes	
Neuropathy	**Acute**	**Subacute of Chronic**
Sensory neuropathy		Diabetes mellitus Leprosy Uremia Alcohol abuse Vitamin deficiency: Vit B1, B6, B12 HIV Hereditary neuropathies Drugs : Cisplatin , Phenytoin Paraneoplatic syndrome
Motor neuropathy	Guillain-Barre syndrome Porphyria Critical illness Poliomyelitis	Chronic inflammatory demyelinating polyneuropathy (CIDP) Lead intoxication

Sensorimotor neuropathy		Diabetes mellitus Uremia Vasculitis Hypothyroidism Paraprotinemias CIDP Drugs Toxins
Autonomic neuropathy	Guillain-Barre syndrome Porphyria	Diabetes mellitus Amyloidosis Familial dysautonomia

Etilogoies based on distribution

1. **Mononeuropathy:**
   - ***Trauma***: most common cause of localized injury to single nerve
   - ***Focal neuropathy***: violent muscular activity, forcible overextension of joint, repeated small traumas
   - ***Pressure or entrapment paralysis:*** affects superficial nerves at bony prominences or at narrow canals; also from tumors, bony hyperostosis, casts, crutches, prolonged cramped postures.
   - ***Haemorrhage*** into a nerve, exposure to cold or radiation
   - ***Tumor invasion***

Multiple mononeuropathy (*mononeuritis multiplex)*:

- ***Collagen vascular disorders*** (polyarteritis nodosa, SLE, Sjörgen's, RA)
- ***Sarcoidosis***
- ***Metabolic diseases*** (diabetes, amyloidosis)
- ***Infectious diseases*** (e.g. HIV, leprosy)

Polyneuropathy:

- Acute febrile diseases: from toxin (e.g. diphtheria), autoimmune reaction (Guillain-Barré syndrome)
- Immunization
- Toxic agents: barbital, phenytoin, heavy metals, carbon monoxide etc.

- Nutritional deficiencies, metabolic disorders: B vitamin deficiency, hypothyroidism, porphyria, sarcoidosis, amyloidosis, uremia, diabetes mellitus.
- Malignancy

Signs and symptoms:

Specific mononeuropathies:

Are characterized by pain, weakness and paresthesias in distribution of affected nerve; multiple mononeuropathy is asymmetric; nerves may be involved all at once or progressively.

Ulnar nerve palsy:

- Often caused by trauma to nerve in the ulnar groove of the elbow, or due to compression at cubital tunnel;
- Paresthesia and sensory deficit in 5th and medial half of the 4th fingers is a common finding.
- Thumb adductor, 5th finger abductor and interossei muscles are weak and atrophied.
- Claw hand deformity may occur.

Carpal tunnel syndrome:

- Is compression of median nerve in volar aspect of wrist, may be unilateral or bilateral.
- Paresthesia in radial-palmar aspect of hand and pain over the wrist and palm; pain may be more severe at night.
- Sensory deficit in palmar aspect of first three fingers may follow; thumb abduction and opposition may become weak and muscles atrophied.
- For all, conservative treatment should be tried first, with surgical exploration taking place if no success or worsening of symptoms occurs.

Radial nerve palsy:

- Is due to compression of nerve against humerus;
- Weakness of wrist and finger extensors (wrist drop),
- Sensory loss over dorsal aspect of 1st finger.

Peroneal nerve palsy:

- It is usually caused by compression of nerve against fibular neck.
- Weakness of foot dorsiflexion and eversion (foot drop) occurs;
- Sensory deficit over anterolateral aspect of lower leg and dorsum of foot or web space between 1st and 2nd metatarsals can occur.

Specific polyneuropathies:

- Are relatively symmetric, often affecting sensory, motor, and vasomotor fibers simultaneously.
- They may affect the axon cylinder or the myelin sheath and, in either form, may be acute (e.g. Guillain-Barré syndrome) or chronic (e.g., renal failure).

Diabetic neuropathy

Sensory polyneuropathy

- Develops slowly over months or years.
- Sensory abnormalities are common, usually starting in the lower extremities, more severe distally than proximally.
- Peripheral tingling, numbness, burning pain, or deficiencies in joint proprioception and vibratory sensation are often prominent.
- Pain is often worse at night and may be aggravated by touching the affected area or by temperature changes.
- In severe cases, there are objective signs of sensory loss, typically with stocking-and-glove distribution.
- Achilles and other deep tendon reflexes are diminished or absent.
- Painless ulcers on the digits or Charcot's joints may develop when sensory loss is profound. Sensory or proprioceptive deficits may lead to gait abnormalities.

Motor neuropathy: results in distal muscle weakness and atrophy.

Autonomic neuropathy: Autonomic nervous system may be additionally or selectively involved, leading to:

- Nocturnal diarrhoea
- Urinary and faecal incontinence and impotence (erectile dysfunction)
- Postural hypotension.
- Vasomotor symptoms vary. The skin may be paler and drier than normal, sometimes with dusky discoloration; sweating may be excessive.
- Trophic changes (smooth and shiny skin, pitted or ridged nails, and osteoporosis) are common in severe, prolonged cases.

Polyneuropathy due to nutritional deficiencies:

- Is commonly seen among alcoholics and the malnourished patients.
- Wasting and symmetric weakness of the distal extremities is usually insidious but can progress rapidly, sometimes accompanied by sensory loss, paresthesia, and pain.

- Aching, cramping, coldness, burning, and numbness in the calves and feet may be worsened by touch.
- Multiple vitamins may be given when etiology is obscure, but they have no proven benefit.

Diagnostic approach to neuropathies

- **History and physical examination**
- **CBC:** e.g. megaloblasts in pernicious anaemia may suggest Vit-B12 deficiency or stippled RBCs indicate lead poisoning.
- **LFT, AP,**
- **Renal function test:** creatinine to assess for renal function test
- **glucose**
- **Urine analysis**
- **Serum protein and electrophoresis** (e.g. multiple myeloma)
- **TFT** if suspicion of thyroid dysfunction
- **Electromyography, nerve conduction velocity tests**
- **Muscle biopsy, sural nerve biopsy** as needed

Treatment:

- Treatment of the underlying cause or systemic disorder; recovery is usually slow
- Traumatic lesions with complete transection of nerve require surgery.
- Entrapment neuropathies may require corticosteroid injections or surgical decompression. Physical therapy and splints reduce the likelihood or severity of contractures.
- If impaired sensation renders the patient prone to injury, protective measures should be taken.
- Autonomic insufficiency is difficult to manage ; orthostatic hypotension can be treated with agents that expand blood volume (e.g. fludrocortisone) and increase vascular tone (epinephrine and yohimbine)
- Tricyclic antidepressants, carbamazepine, phenytoin and capsaicin can help patients suffering room pain.

Guillain-Barré syndrome

Definition: also called Landry's ascending paralysis

- It is an acute inflammatory demyelinating polyradiculoneuropathy.

- It is predominantly motor neuropathy characterized by muscular weakness and arflexia (loss of deep tendon reflexes)
- It has an acute onset and it is usually rapidly progressive in nature.
- There may be also mild distal sensory loss.

Etiology and pathogenesis:

The etiology is not known but it is believed to be due to autoimmune damage to the myelin sheath of peripheral nerves.

In about 2/3 of cases, the disease begins 5 days to 3 wk following an antecedent event such as:

- *Non specific viral syndrome*
- *May be associated with HIV infection*
- *Campylobacter jejuni infection*
- *Hepatitis , infectious mononucleosis*
- *Mycoplasma pneumonae infection*
- *Vaccination*
- *Surgery*
- *Lymphoma or*
- *SLE*

It is the most common acquired demyelinating neuropathy.

Signs and symptoms:

- Relatively symmetric weakness with paresthesia usually begins in the legs and progresses to the arms.
- Weakness typically evolves over hours to a few days, and for 90% of patients, weakness is maximal at 3 wk after which the patent reaches a plateau, and further progression is unlikely.
- Weakness is always more prominent than sensory abnormalities and legs are usually more affected than the arms.
- Deep tendon reflexes are lost.
- Sphincters (both bladder and bowel) are usually spared.
- More than 50% of patients with severe disease have weakness of facial muscles (diaparesis).
- The lower cranial nerves are also frequently involved, causing bulbar weakness and difficulty of swallowing difficulty of handling secretions and maintaining the airways.

- Most patients need hospitalization, and almost 30 % require ventilator assistance at some time during their illness due to possible respiratory failure.
- Autonomic dysfunction: wide fluctuation in BP, postural hypotension, and inappropriate ADH secretion, cardiac arrhythmias and pupillary changes occur in severe cases. These complications need close monitoring as they may be fatal.
- Pain is another common feature of GBS. The usual type of pain is deep aching pain in the weakened muscles. Back pain involving the entire spine may also be felt.
- Respiratory paralysis and autonomic dysfunction may be life-threatening.
- About 5% of patients die.

Diagnosis:

- ***Presumptive diagnosis is made based on history and physical examination.***
- ***CSF analysis:*** elevated protein but few (<50 mononuclear cells) or no cells not cells (albumino-cytologic dissociation).
- ***Nerve conduction test (NCT):*** slow nerve conduction velocity, evidence of conduction block, and prolonged distal latencies, which suggest demyelination is the usual finding.

Differential diagnosis:

- Toxins (organic phosphate, botulism),
- Acute poliomyelitis.

Treatment:

Guillain-Barré syndrome is a medical emergency, requiring constant monitoring and support of vital functions.

General supportive measures:

- The airway must be kept clear, and vital capacity should be measured frequently, so that respiration can be assisted if necessary.
- Fluid intake should be sufficient to maintain a urine volume of at least 1 to 1.5 L/d.
- Extremities should be protected from trauma and from the pressure of bed rest.
- Heat helps relieve pain, making early physical therapy possible.
- Immobilization, which may cause ankylosis, should be avoided. Passive full-range joint movement should be started immediately and active exercises begun when acute symptoms subside.
- Heparin 5000 U SC BID may help to avoid thromboembolism in bedridden patients.

Immunotherapy:

- ***Plasmapheresis:*** can shorten the length of time that the patient is dependent on respirator and unable to ambulate. Criteria to initiate plamapheresis include the inability of the patient to walk or rapid progression of the diseases.
- ***Immunoglobulin treatment:*** it is also effective and decreases morbidity and hastens recovery.

  Plasmapheresis and immunoglobulin treatment may be given in combination
- ***Steroids are not effective in GBS***, but in chronic relapsing Polyneuropathy, corticosteroids improve weakness and may be needed for a long time. Immunosuppressive drugs (azathioprine) and plasmapheresis benefit some patients.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Nerve and muscle dioders, pages 2500-2540.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Neuropathy: pages 638-640.

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8. CNS infections

I. Pyogenic (bacterial) meningitis

***Learning Objective**:* At the end of this unit the student will be able to

1. *Define Bacterial meningitis.*
2. *List the etiologies of Bacterial meningitis.*
3. *Describe the mode of transmission Bacterial meningitis.*
4. *Describe the epidemiology of Bacterial meningitis.*
5. *Identify the clinical features of Bacterial meningitis.*
6. *List the common complications of Bacterial meningitis.*
7. *Describe the most commonly used tests for the diagnosis of Bacterial meningitis.*
8. *Make an accurate diagnosis of Bacterial meningitis.*
9. *Understand the management of Bacterial meningitis.*
10. *Understand methods of prevention Bacterial meningitis.*

Definition: is an inflammation of the arachnoid layer of the meninges and the fluid that circulates, in the ventricles and sub-arachnoid space (CSF), caused by bacterial infection

Etiologic agents: the causes of bacterial meningitis vary with age:

- ***Infants (< 1 year)***: *E. coli, group-B streptococcus, Listeria monocytogenous* are the commonest causative agents.
- ***Young children/toddlers (age 1- 6 years)*** : *Haemophilus influenza, Meningococcus* account for > 50 % of cases
- ***Adolescents and Adults:*** *Meningococcus, Pneumococcus* are the commonest etiologies
- ***In immunocompromised hosts and cancer patients***: *Listeria, Staphylococcus, Pseudomonas aeruginosa* etc.

Rout of infection:

- ***Droplet infection through the upper airways:*** E.g. In *Meningococcus meningitis,* with possibly epidemic spread
- ***Haematogenous spread:*** e.g. in Pneumococcus pneumonia
- ***Contagious spread from adjacent sites :*** e.g. in otitis media , sinusitis

- ***Direct:*** e.g. in open head injury

Epidemiology:

- Bacterial meningitis is the most common form of suppurative CNS infection.
- In the West due to the availability of vaccines for *N. meningitidis* and *H. influenza, S. pneumonae* has become the leading cause of bacterial meningitis.
- However, in African and most developing countries, *N. meningitidis* is still the leading cause of bacterial meningitis in adolescents and adults. An outbreak of meningitis epidemic has been documented to occur every 7- 10 years in the meningitis belt in African, which includes our country Ethiopia.

Clinical presentation;

- **Incubation period:** the incubation period for Meningococcal meningitis may range from 1-10 days, but mostly the clinical manifestations occur within in 2-4 days
- Meningitis may manifest as an acute fulminant illness that progress rapidly in few hours or as a subacute infection that progressively worsens over several days.
- The classic clinical triad of meningitis is ***fever, headache and nuchal rigidity (neck stiffness)*** , which are seen in > 90 % of patients .
- Alteration in metal status can occur in > 75 % of patients and can vary from lethargy to comma.
- Nausea and vomiting are common symptoms.
- Avoiding light (photophobia) is seen in some patients.
- Seizure occurs as part of the initial presentation of bacterial meningitis, or during the course of the illness in 20-40 % of patients
- In Meningococcal meningitis of sudden onset with severe course, patients develop diffuse erythromatus maculopapular rash which rapidly becomes petechial, purpural or bullos lesions. The petichiae are found on the trunk, lower extremities, in the mucous membrane and the conjunctiva, and occasionally on the palms and soles.
- In older and debilitated patients the symptoms of meningitis may be subtle.

Meningeal signs are clinical signs often sound in patients with meningitis

- ***Neck stiffness*** when head is flexed passively
- ***Kerning's sign***: when one leg which is flexed at the hip and knee joints, is passively extended at the knee joint, the other leg flexes at the knee.
- ***Brudzinski's sign:*** Upon passively flexing the head, one notices flexion of both legs at the knees

Note: These classic meningeal signs may not be seen in infants, old persons and patients in coma.

Complications:

- Brain edema,
- Hydrocephalus
- Brain abscess,
- Septic vein thrombosis
- Hearing impairment
- Fulminant meningococcal sepsis: Waterhouse-Friedrichsen syndrome is a clinical condition resulting from hemorrhagic necrosis of the adrenal gland, with multi-organ failure. Patients are hypotensive or in shock. Disseminated intravascular coagulation (DIC) with skin and mucosal purpura and bleedings are commonly seen associated features.

Diagnostic approach

- History, physical examination,
- Search for possible source of infection(pneumonia , otitis media , sinusitis , head injury)
- CSF analysis
- Identify the organism from CSF and blood (culture, PCR etc.)
- Serologic antibody test : latex agglutination test

Laboratory findings:

General signs of inflammation: leukocytosis, CRP and ESR ↑

CSF analysis:

- Gross appearance and opening pressure : CSF looks turbid and the opening pressure is increased (due to raised intra cranial pressure)
- Cell count and differential : polymorphonuclear leukocytosis
- Biochemical tests : glucose is decreases and protein in the CSF is elevated
- Gram stain Culture and sensitivity
    - Meningococcus are seen as gram negative intracellular diplococcic

***Table VIII-8-1, CSF analysis findings in different types of meningitis* .**

	Bacterial meningitis	**Viral meningitis**	**Tuberculous meningitis**
Appearance	Turbid	Clear	Cob-web appearance
Cell count/µl	Several thousand	Several hundreds	Several hundreds
Cell type	Granulocytes(PMNLs)	Lymphocytes	Lympho-, monocytes
Glucose	↓ (< 30 mg/dl)	Normal	↓ (< 30 mg/dl)
Protein	↑ (> 120 mg/dl)	Normal	↑ (> 120 mg/dl)
Lactate dehydrogenase (LDH)	> 3.5 mmol/L	< 3.5 mmol/l	> 3.5 mmol/l

Differential diagnosis:

- Virally caused meningoencephalitis (Coxsackie-, Echo-, Mumps-virus, HIV, measles, CMV, VZV, HSV)
- Chronic meningitis : Tuberculous meningitis , Cryptococcal meningitis
- Subarachnoid hemorrhage

Treatment:

A. Antibiotic Therapy

1. Empirical antibiotic therapy:

Bacterial meningitis is a medical emergency and antibiotics should be initiated immediately before the results of the CSF gram stain and culture are known.

Antibiotics should be given intravenously, at higher doses

- In adults without underlying disease: Ceftriaxone 2 gm IV BID plus Ampicilline 2 gm IV QID for 2 weeks.
- Crystalline Penicillin 3-4 million IU, IV every 4 hours plus Choramphnicole 1gm IV QID are alternative antibiotics for a resource limited setting .
- Patients with ENT infection or head injury: Ceftriaxone 2 gm IV BID and Vancomycin 1 gm IV BID + treatment of the underlying cause.
- If suspected hospital-acquired infection: Ceftriaxone 2 gm IV BID plus Vancomycin 1 gm IV BID plus Gentamycin (80 mg TID)
- In immunodeficient patients: Ceftriaxone 2 gm IV BID plus Vancomycin 1 gm IV BID plus Ampicillin (2g IV QID)

2. ***Specific antibiotic therapy***: is given when the specific etiologic agent is identified through gram stain or culture

- ***N. meningitidis*** *:* Even though Ceftriaxone or Cefotaxim provide adequate empirical coverage , Penicillin G remains the drug of choice for *N. Meningitides*
  Crystalline Penicillin 3-4 million IU, IV every 4 hours for 7 -10 days may be adequate.
- ***Pneumococcal meningitis***: Antibiotic therapy in initiated with Cephalosporins plus Vancomycine
  Ceftriaxone 2 gm IV BID and Vancomycin 1 gm IV BID for 2 weeks
- ***H. influenza*** : Ceftriaxone 2 gm IV BID for 1- 14 days may be enough
  Choramphnicole 1gm IV QID may be an alternative antibiotic, for patients who may not afford Ceftriaxone.

B. Symptomatic and adjunctive Therapy

- ***Steroids:***
  - ***Dexamethason*** when initiated before antibiotic therapy reduces the number of unfavourable outcomes, including death and neurologic complications. It is mainly advantageous in children, predominantly with meningitis due to *H. Influenza and S. Pneumoniae.*
    Dose*:* Dexamethason10 mg IV 15-20 minutes before the first dose of antibiotics and 4 mg IV QID for 4 days
- ***Treat increased intracranial pressure*****:**
  - Elevation of the patients head to 30-45^{o}
  - Intubation and hyperventilation (till $PaCO_2$ is lowered to 25-30 mmHg)
  - Mannitol IV infusion
- ***Regulate water and electrolyte balance,***
- ***Thromboembolism prophylaxis***
- ***Patients with meningococcal meningitis should be isolated***.

Chemoprophylaxis: In case of *N. Meningitides,* all close contact to the patient should be given chemoprophylaxis with:-

- Rifampicin 600 mg PO BID for 2 days in adults and 10mg/kg PO BID for children > 1 yr.
- Ciprofloxacin 750 mg PO stat can be given as an alternative for adults.

II. Viral encephalitis

***Learning Objective**:* At the end of this unit the student will be able to

1. *Define viral encephalitis.*
2. *List the etiologies of viral encephalitis.*
3. *Identify the clinical features of viral encephalitis.*
4. *Describe the most commonly used tests for the diagnosis of viral encephalitis.*
5. *Understand the management of viral encephalitis.*

Definition: Inflammation of the brain parenchyma, with or without involvement of the meninges, caused by virus. The spinal cord and/or nerve roots may also involved rarely.

Signs and symptoms:

- Acute febrile illness with evidence of meningeal involvement (meningeal signs)
- Altered level of consciousness (ranging from lethargy to coma)
- Abnormal mental state (hallucinations, agitation, personality change, behavioural disorder, psychosis)
- Evidence of either focal or diffuse neurologic signs or symptoms.
- Focal or generalized seizures occur in > 50 % of cases.
- Most common focal findings are aphasia, ataxia, hemiparesis (with hyperactive tendon reflexes), involuntary movements and cranial nerve deficits.

Organisms: Viruses causing encephalitis

Common	**Less common**	**Rare**
Arboviruses, enteroviruses, HSV-1, mumps	CMV, EBV, HIV, measles, VZV	Adenoviruses, CTFV, influenza A, LCMV, parainfluenza, rabies, rubella

Laboratory findings:

- ***CSF examination:*** check for increased intracranial pressure first. Characteristic profile is undistinguishable from viral meningitis and consists of lympocytic pleocytosis, elevated protein, normal glucose level
- CSF PCR, if available
- CSF culture, usually negative (esp. in HSV-1 infections)
- Serologic studies and antigen detection, if available
- MRI, CT, and EEG: if available, done to exclude alternative diagnoses, and assist in differentiation between focal and diffuse encephalitic process (e.g. 90 % of patients with HSV-1 infection have abnormalities in the temporal lobe on MRI).
- ***Brain biopsy:*** reserved for patients with unclear diagnosis, lack of response to therapy and who have abnormalities on imaging techniques.

Treatment:

Supportive therapy (usually in ICU):

- Check vital signs, restrict fluid, and give antipyretics.
- Treat seizures and/or give prophylactic therapy (high risk for seizures!).

Medication:

- Acyclovir 10 mg/kg TID for at least 14 days (adult dose).
- Gancyclovir (5 mg/kg BID) or Foscarnet (60 mg/kg TID) are especially recommended for CMV infections.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Meningitis and Encephalitis , pages 2471-2489.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, CNS infections, pages 644-645.

CHAPTER NINE
CONNECTIVE TISSUE DISORDERS AND DISEASES OF THE JOINTS

Overview:

These are a group of medical disorders resulting from immunologic damage to the connective tissue of the body.

They overlap with each other, may affect many organ systems, and often respond to immunosuppressives. Their pathologies vary.

The following are some of connective tissue disorders:

1. Systemic lupus erythematosus (SLE),
2. Rheumatoid arthritis
3. Systemic sclerosis (Scleroderma)
4. Polymyositis
5. Mixed connective tissue Disorder
6. Primary Sjörgen's syndrome
7. Behçet's disease.

1. Systemic lupus erythematosus (SLE)

Definition: SLE is a chronic immune disorder characterized by multisystem involvement and clinical exacerbations and remission.

Circulating immune complexes and autoantibodies cause tissue damage and organ dysfunction.

Epidemiology:

- The prevalence of SLE is approximately 15-5- cases per 100, 000 population
- The prevalence in young women of child bearing age is 8- 10X that of men (F: M ratio is 8:1 – 10:1)
- More common in black women than white women , more common in pregnancy
- SLE has familial tendency and the concordance rate among identical twins is 50 %

Etiology: No single cause identified for SLE, it results from complex interaction of environmental, genetic factors and hormonal influences

1) Environmental factors: virus and drugs or toxins. It may be induced by drugs (isoniazid, hydralazine, chlorpromazine etc.)
2) Genetic factors : there is genetic predisposition to SLE
3) Autoimmunity : loss of tolerance to autoantigens is central to the pathogenesis
4) Hormonal influence : as the disease is more common in women of child bearing age , estrogen may play a role in the pathogenesis

***Clinical features :*Signs and symptoms:**

a) **Systemic symptoms:** Fatigue , weight loss and fever are prominent systemic complaints

b) **Skin:**

- Photosensitive malar butterfly rash(facial erythema over the cheeks and nose) ,
- The chronic potential scarring discoid lesions, alopecia,
- Livedo reticularis, Raynaud's phenomena, purpura, oral ulcers, urticaria, conjunctivitis, bullae.

c) **Musculoskeletal:**

- Joint/muscle pain, non-erosive polyarthritis
- Myositis, proximal myopathy,
- Aseptic bone necrosis

d) **Renal:** SLE cause diffrent types glomerulonephritis which may manifest with proteinuria, casts, edema, and later on to Cronic renal failure (uremia)

e) **CNS:** Focal or diffuse neurologic disordrs occur in approximatly 50 % of pateints

- ***Generalized manifestations*** : Severe headache, reactive depression, psychosis, seizure , and cognitive disturbance
- ***Focal:*** focal seizure, hemiparesis, paraparesis, cranial nerve lesions, ataxia, chorea may also be seen.
- ***Peripheral nerves***: some pateints may have sensory or senorimotor neuropathies

f) **Lung:**

- Pleurisy,
- Lupus pneumonitis,
- Fibrosing alveolitis

g) **CVS:**

- Hypertension from renal involvment

- Pericarditis,
- Non infective endocarditis
- Myocarditis
- Coronaty vessle Vasculitis

h) **Blood:** anemia, leukopenia, lymphopenia, thrombocytopenia, increased ESR

i) **Gastrointestinal tract:** intestinal vasculitis , Pancreatitis

j) **Other:** fever, splenomegaly, lymphadenopathy, recurrent abortion

Diagnosis:

1) **Hematology:** Anemia, elevated ESR, decreased platelet count

2) ***Urinalysis:*** proteinuria, hematuria

3) ***Renal function test***: BUN and creatinin may be elevated

4) ***Serology***

- ANA (antinuclear antibodies) nearly 99 % of patients with SLE have ANAs
- Antibodies against double-strand DNA
- Low complement components (C3 and C4)

Treatment:

1) If the SLE is believed to be due to be drug-induced, stop the drug.

2) Give sun-block creams or sunscreens

3) ***NSAIDs*** are used in full anti inflammatory dose for fever, joint complaints and serositis.

4) Hydroxychloroquine if joint/skin symptoms are not controlled by NSAIDs, e.g. 400 mg/d PO for 6 mo, then 200 mg/d.

5) ***Corticosteroids*** :

- High-dose predenisolone in life-threatening conditions, 1 mg/kg/d for 6 wks, then taper. May be combined with other immunosuppressives.
- Low-dose predenisolone is of value in chronic disease.

6) Cytotoxic drugs: (E.g. azathioprine, cyclophsphamide) sometimes are employed to treat severe refractory features of SLE, particularly renal diseases.

Prognosis

- Early diagnosis and treatment decreases morbidity and mortality
- Renal diseases and infectious complications are the major causes of death
- CNS diseases can lead to severe disability

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Asthma, pages 1508-1515
2) Myers R. Allen , National Medical Series for independent Study (NMS) 3rd edition Medicine, Asthma, pages 75-78

2. Rheumatoid Arthritis (RA)

Learning objectives: at the end of this lesson the student will be able to:

1) *Define Rheumatoid arthritis*
2) *Describe the etiology and pathogenesis of Rheumatoid arthritis*
3) *Identify the clinical features of Rheumatoid arthritis*
4) *Understand the diagnostic approach and investigations for Rheumatoid arthritis*
5) *Understand the management principles of Rheumatoid arthritis*
6) *Describe prognostic factors for Rheumatoid arthritis*

Definition: it is a chronic multisystemic inflammatory disease of unknown cause, characterized by persistent inflammatory synovitis, usually involving peripheral joints in a symmetrical distribution. The potential of the synovial inflammation to cause cartilage damage and bone erosion and subsequent changes in joint integrity is the hall mark of the diseases.

Epidemiology

- The prevalence of RA is approximately 0.8 in the population.
- Women are more affected than men with F: M ratio of 3:1
- The prevalence increases with age and, and the sex difference diminishes in the older age group.

Etiology:

Te cause of RA remains unknown. It is suggested that RA may be a manifestation of a response to an infectious agent in a genetically susceptible host.

1) ***Genetic factors*** : genetic susceptibility to altered immune response may play a role
    - The concordance rate among monozygotic twins is 4X, and first degree relatives of patients with RA have a very high chance of developing RA
    - The presence of HLA-DR4 allogen is associated with high incidence of RA.
2) ***Infectious agent***: may play a role in triggering an autoimmune reaction. Infectious agents such as rubella, Mycoplasma, CMV and EBV virus may play a role in the pathogenesis

Clinical Features

Onset:

- ***Insidious onset***: in about 2/3 of patients the RA begins insidiously with prodromal nonspecific symptoms such as fatigue, weight loss, anorexia, generalized body

weakness and vague musculoskeletal symptoms, for weeks or months before the occurrence of specific joint symptoms.

- ***Acute onset:*** in about 10 % of patients RA has an acute onset, with rapid development of polyarthritis, associated with constitutional symptoms, including fever, lymphadenopathy and splenomegaly.

1) ***Articular (joint) manifestations:*** result from persistent inflammatory synovitis

- Pain , swelling and tenderness of involved joints , aggravated by movement
- Generalized joint stiffness is often seen after a period of inactivity. Morning stiffness which lasts greater than 1 hr, which is a feature of inflammatory arthritis is a common complaint.
- Bilateral, symmetrical small joint involvement is typical for RA

Commonly affected joints are:-

- ***Wrist joints, Metacarpo phalangal joints (MPJ) and proximal interphalangal PIP) joints*** are often involved but distal interphalangal (DIP) joints are often spared. The elbow joint , and keen joints are also affected by RA.
- ***Wrist joint :*** synovitis of wrist joint is very common is RA , and may lead to limitation of movement , deformity and median nerve entrapment (Carpal tunnel syndrome)
- ***Elbow joint*** involvement may lead to flexion contracture
- ***Keen joint*** is commonly involved with synovial hypertrophy, chronic effusion and frequent ligamentous laxity. Pain and swelling behind the knee may be caused by extension of inflamed synovium in to poplitial space (Baker's cyst)
- ***Arthritis of the forefoot, ankles and subtalar joints*** can produce sever pain with ambulation and as well as a number of deformities.
- ***Axial involvement is limited to cervical spines*** ; Atlantoaxial ligament involvement , in the cervical spine can lead to instability between C1 and C2 vertebrae and potential neurologic complaints

Joint deformities: with persistent inflammation, a variety of characteristic joint changes develop due to damage or weakening of ligaments, tendons and joint capsule. These deformities include:-

- ***Z- deformity:*** radial deviation at the wrist with ulnar deviation of the digits
- ***Swan neck deformity***: hyperextension of the PIP joints, with compensatory flexion of DIP joints
- ***Boutonier deformity***: Flexion contracture of PIP joints and extension of DIP joints

2) ***Extraarticular features :*** RA is a systemic diseases with a variety of extraarticular manifestation

- Although these occur frequently, not all of them has clinical significance. However, occasionally they may be the major evidence of disease activity and source of morbidity.
- More often, these manifestation occur in patients who have high titer of rheumatoid factor and patients who have more severe and established diseases

a) Rheumatoid nodules: are the most common features of extraarticular diseases and are found in 20-25 % of patients.

These firm subcutaneous masses typically are found in areas on periarticular structures and on areas exposed to of repetitive trauma (e.g. extensor surface of the forearm, the olecranion at the elbow, proximal ulna, Achilles tendon and the occipit).

In some patients rheumatoid nodules may be found on the viscera (e.g. lungs, meningitis)

b) Rheumatoid vasculitis: This can affect nearly any organ system and is seen in patients with severe RA, and high titer of circulating Rheumatoid factor.

- ***Peripheral nerves*** : Distal sensory neuropathy or Mononuritis multiplex
- ***Skin:*** cutanous ulceration , dermal necrosis
- ***Digital gangrene***
- ***Visceral infarction*** : Myocardial infarction , vasculitis involving the lungs , bowel , liver, spleen, pancreas ,kidneys etc

c) Eye involvement :

- ***Keratoconjuctivitis sicca is seen*** in 10% -15 % of rheumatoid arthritis patients who have a secondary form of Sjogren syndrome
- ***Scleritis or episcleritis*** occur less common

d) Lungs

- ***Pleuritis and pleural effusion*** may be seen is some patients. The pleural fluid typically has low glucose concentration.
- ***Intestinal fibrosis***
- ***Rheumatoid nodules*** may appear on the lung, single or multiple.

e) Heart

- ***Asymptomatic Pericardits*** is fund in 50% of patients on autopsy. It is often associated pleural effusion.
- ***Myocarditis and Valvular dysfunctio***n are rare findings

f) Neurologic manifestations : the CNS is not directly affected

- ***Peripheral nerves are affected*** through Entrapment (carpal tunnel syndrome) or Vasculitis related mononuritis multiplex
- ***Atlantoaxial sublaxation*** : may lead to compression of spinal cord

g) Hematologic features

- Anemia of chronic diseases
- Thrombocytosis
- Felty's syndrome: chronic RA with splenomegaly and neutropenia, with an occasional thrombocytopenia and anemia. ,

Constitutional symptoms: like weight loss, fever anorexia and fatigue are common complaints and may be severe in patients with extraarticular manifestations

Diagnostic approach for RA

1) Proper history taking and Physical examination play a crucial role in making the diagnosis of RA

2) Laboratory findings

a) Hematology: CBC may show normocytic, normochromic anemia, leukocytosis and thorombocytosis. ESR is often raised indicating chronic inflammation

b) Rheumatoid factor: It is autoantibodies against the Fc component of IgG. It is typically present in 60 % of patients in the first year and 80% of patients with long standing diseases. Note that 30 -40 % of patients with rheumatoid arthritis may be sero-negative for Rheumatoid factor.

3) Radiographic findings :

- ***Early*** characteristic changes include soft tissue swelling and loss of bone in periarticular areas (periarticular osteopenia).
- ***Late:*** sustained inflammation leads to loss of bones at joint margins (erosion) and joint space narrowing as a result of cartilage loss and joint deformity.

Revised American revised Criteria for classification of RA

1) *Morning stiffness: lasting > 1 hr*

2) *Arthritis of three or more joint areas:*

3) *Arthritis of hand joints: wrist, MCP and PIP*

4) *Symmetrical athirst*

5) *Rheumatoid nodules: subcutaneous nodules over bony prominences*

6) *Serum rheumatoid factor*

7) *Radiologic changes : periarticular bony erosion and other fndigs*

Interpretation:

- Four of seven criteria are required to classify a patient as having Rheumatoid arthritis
- Patients with two or more criteria, the clinical diagnosis of RA is not excluded.

Therapy

Goals of therapy:

1. ***Short term*** : Controlling pain and reducing inflammation without causing undesired side effects
2. ***Long term***: Preservation of joint function and the ability to maintain life-style.

A) Pharmacotherapy

1) ***First line Treatment:*** **NSAIDs (Non steroidal anti-inflammatory drugs):** are the first line drugs.
   - They are used to control symptoms and signs of local inflammatory process.
   - These agents are rapidly effective in alleviating pain and symptoms , but there effect on long term disease progression is minimal.
   - Aspirin, Ibuprofen, diclofenac, indometacin may be used

   Dose: Aspirine 900 mg PO TID, Ibuprofen 400 mg PO BID or Diclofenac 50 mg PO BID or TID

   Side effects: Dyspepsia, PUD, Renal dysfunction, bone marrow toxicity.
2) ***Second line treatment:*** low dose oral Corticosteroids have potent anti-inflammatory effect , but they have equally predictable unwanted side effects.
   - **Systemic administration:** are given in sever progressive articular diseases and extra articular involvement

     Dose: start 5-10 mg once daily in the morning. If patients improve, attempt should be made to taper the dose.
   - ***Local injection:*** steroids may be injected occasionally to joints which are severely affected
3) ***Third line: Disease modifying antirheumatic drugs- or slow acting antirheumatic drugs (DMARD)***
   - This group of agents include Methotrexate , gold compounds , D-penicillamine , antimalarials and sulfasalazine

- These are drugs which have no analgesic effect and generally require weeks to months before anti-inflammatory effects are evident. Hence, NSAIDs should continue during the administration of DMARDs.
- They have the capacity to alter the course of RA.
- They are used in patients with rheumatoid arthritis, who are not responding to NSAIDs (with or without steroid).
- These drugs may be used singly mostly, but they may be prescribed in combinations in patients with bad prognosis or refractory diseases.
- The disease progression is delayed with these drugs and acute phase reactants such as ESR and C-reactive proteins frequently decline.

Methotrexate is the most frequently DMARD used, which is relatively rapidly acting

Dose: given in an intermittent low dose: 7.5-30 mg once weekly

Side effects: GI upset, oral ulcer, liver function abnormalities and insidious liver fibrosis.

Administration of folic acid or folinic acid may diminish the frequency of some side effects,

4) ***Fourth line: Anti cytokine agents:*** this are biological agents that bind and neutralize TNF. These drugs are effective in controlling signs and symptoms of RA in patients who ailed to respond with DMARDs.

5) ***Fifth line : immunosuppressive therapy :***

These include drugs such as Azathioprine, cyclsosporine, and cyclophosphamide.

They have the same therapeutic effect as DMARDs, but they are not more effective than DMARDs

They are prescribed to patients who fail to respond to DMARDs

B) Non pharmacologic therapy

1) ***Patient education:;***

- Description of the illness : the chronicity of the diseases
- Rest and exercise
  a. Patients should be advised to rest or splint acutely involved joints
  b. Exersise is advised to srenghten muscle surrounding involved joints , when the arthritis is resolved

2) ***Physiotherapy and occupational therapy*** to reduce disability

Assessment of response:

- ***Resolution of symptoms***: reduction or disappearance of joint pain, stiffness and swelling
- ***Functional status:*** ability of the patient to perform daily activities and living
- ***Laboratory:*** anemia may be corrected and ESR declines

Surgical therapy:

- ***Early:*** synovectomy may decrease the inflammatory process in joints or tendon sheaths that remain inflamed despite drug therapy
- ***Late:*** artheroplasy or total joint replacement may be appropriate to relive pain or help restore function in structurally deformed joints.

Prognostic factors: poor prognostic factors include

- Many persistently inflamed joints
- Poor functional status
- Low educational status of the patient
- Rheumatoid factor positivity
- HLA-DR4 positivity
- Extra-articular diseases
- Persistently elevated acute phase reactants (ESR, C-reactive protein)
- Radiologic evidence of erosion

References:

3) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Asthma, pages 1508-1515
4) Myers R. Allen , National Medical Series for independent Study (NMS) 3rd edition Medicine, Asthma, pages 75-78

3. Other connective tissue diseases

3.1. Systemic sclerosis (Scleroderma)

It is defined as a connective tissue characterized by widespread small vessel obliteration disease and fibrois of the skin and multiple internal organs.

Classification:

- **Limited cutaneous systemic sclerosis:** formerly called CREST syndrome (**c**alcinosis, **R**aynaud's, **e**sophageal motility disorder, **s**clerodactyly and **t**elangeictasia).
- **Diffuse cutaneous systemic sclerosis** with skin, renal and gut involvement; associated with malignant hypertension, Raynaud's and myocardial disease. No effective treatment known.
- **Localized (morphea=localized scleroderma):** localized skin sclerosis, progresses rarely. Characteristic antibodies: topoisomerase, RNA polymerase, centromeres.

3.2. Primary Sjörgen's syndrome

Definition: Association of a connective tissue disease (in 50 % rheumatoid arthritis) with keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth) due to lymphocyte and plasma cell infiltration into secretory glands.

Signs and symptoms:

- Dry eyes, mouth
- Dyspareunia
- Dry skin
- Dysphagia
- Otitis media
- Pneumonia
- Other: neuropathy, renal involvement, hepatosplenomegaly, drug reactions, lymphoma, decreased well-being (headaches, GI symptoms, decreased concentration).

Diagnosis:

- History and physical examination
- Schirmer's test to quantify tear production
- Biopsy of salivary glands

Treatment: artificial tears, occlusion of punctum which drains tears. Xerostomia may respond to frequent cool drinks or artificial saliva spray.

3.3. Idiopathic myopathies: polymyositis and dermatomyositis

Definition: polymyositis is an idiopathic inflammatory muscle diseases characterized by insidious, symmetrical, prominent proximal muscle weakness resulting from muscle inflammation, elevated muscle enzymes and characteristic EMG finding.

- **Signs and symptoms:**
- ***Skin***: The rash of dermatomyositis consists of erythematous paths which sometimes are scaling or atrophic and distributed over the face and, neck and upper chest and extensor surfaces. Rash on cheeks, eyelids and light-exposed areas may be seen.
- ***Lung:*** Chronic interstitial lung diseases
- ***Joint:*** mild symmetrical inflammatory arthritis
- ***Muscles***: most patients have gradual but steady progression of muscle weakness. Some patients may have fulminant course that acute respiratory failure or myoglobinurin acute renal failure can ensue.
- ***Pharyngeal muscle weakness*** can lead to a problem in swallowing and aspiration and respiratory muscle dysfunction. Patients may have also dysphonia, facial edema.
- ***Other features***: retinitis and myocardial involvement may occur.

Diagnosis:

- Muscle enzyme (CK)is elevated
- EMG (electromyography) shoe characteristic features
- Muscle biopsy.

Treatment: Rest, prednisolone (start with 1 mg/kg/d PO), other immunosuppressives.

3.4. Mixed connective tissue disease

- MCTD combines features of SLE, systemic sclerosis and polymyositis. Renal or CNS involvement is rare.
- Antibodies against ribonuclear protein are present.

- Treat with immunosuppressives including steroids.

3.5. Relapsing polychondritis

- Relapsing polychondritis attacks pinna, nasal septum and larynx, the last causing stridor.
- It is associated with aortic valve disease, arthritis and vasculitis.
- Treat with steroids.

3.6. Behçet's disease

Definition: A multiorgan disease associated with certain HLA-types and thromboses.

More common in men M:f=2:1.

Signs and symptoms:

- ***Joints:*** arthritis
- ***Eyes:*** pain, decreased vision, floaters, iritis, retinal vein occlusion
- ***Mouth, scrotum, labia***: painful ulcers, heal by scarring
- ***Gut:*** colitis
- ***CNS:*** meningoencephalitis, increased intracranial pressure, brainstem signs, dementia, myelopathy, encephalopathy, cerebral vein thrombosis.

Treatment: Colchicine, steroids (topical and oral), other immunosuppressives.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Connective tissue diseases , pages 1979-2015.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, pages 570-581.

4. Gout

Learning objectives: at the end of this lesson the student will be able to:

1) *Define Gout*
2) *Describe the etiology and pathogenesis of Gout*
3) *Identify the clinical features of Gout*
4) *Understand the diagnostic approach and investigations for Gout*
5) *Understand the management principles of different types Gout*

Definition: A group of disorders of purine metabolism that are characterized by serum uric acid elevation (hyperuricemia), urate deposits in articular or extraarticular tissues.

Elevation of serum uric acid alone is not sufficient for the diagnosis of gout; only 10 % of patients with hyperuricemia develop gout. Some unknown factors predisposes some patients to urate deposition and articular inflammation, in the setting of sustained hyperuricemia

Etiologic classification of Hyperuricemia

All gout syndromes are characterized by either episodic or constant elevation of serum uric acid concentration above 7 mg/dl. Patients with elevated serum uric acid are mainly due to

1) ***Overproduction:*** account for 10 % of patients. These patients synthesize greater than normal amount of uric acid de novo. The urinary excretion of urate is >1000mg/day (they have normal urinary excretion of uric acid). The defect causing uric acid overproduction may be :-
   a) ***Primary***: purine pathway enzyme defect
   b) ***Secondary :*** increased cell turn over or cellular destruction associated with alcohol use, hematologic malignancies , chronic Hemolysis , or cancer chemotherapy
2) ***Under secretion of Uric acid***: account for 90 % of patients. Decreased renal excretion of uric acid is the underlying reason for hyperuricemia (urinary excretion of uric acid is < 700mg/dl)
   a) ***Drugs:*** Diuretics , alcohol , Aspirin interfere with tubular handling of urate
   b) ***Renal diseases*** ; chronic renal failure , lead nephropathy , inherited disorders

Conditions associated with Gout

- ***Obesity:*** serum uric acid level rises with body weight
- ***Diabetes mellitus***: more common in gout 576 patients
- ***Hypertension:*** is more common in gout patients
- ***Hyperlipidemia***
- ***Atherosclerosis***

Clinical Stages of gout

a) ***Asymptomatic hyperuricemia*** : is characterized by an increased serum uric acid level in the absence of clinical evidences of deposition diseases (i.e. arthritis , tophi , nephropathy or uric acid stones)
   - These patients have an increased risk of having nephrolithiasis or acute obstructive uropathy

b) ***Acute gouty arthritis :*** is the second and primary manifestation of gout – is an extremely painful , acute onset arthritis
   - Most patients (80-90 %) are middle aged or elderly men who have had sustained asymptomatic hyperuricemia for 20-30 yrs before the first attack.
   - Premenopausal women are not affected by gouty arthritis, perhaps due to the effect of estrogen on uric acid clearance. However gout may be seen in postmenopausal elderly women who have mostly associated hypertension.
   - Onset of acute gouty arthritis in teens or 20s is unusual, and when it occurs it is often associated with primary or secondary causes of uric acid overproduction.
   - Several events may precipitate acute gouty arthritis including: dietary excess, trauma, surgery, excessive alcohol ingestion, ACTH or glucocorticoid withdrawal, hypouricemic therapy and serious medical illnesses like myocardial infarction and stroke .
   - ***Presentation:*** an acute onset of severe, painful and tender joint swelling, affecting the first Metatarsoplalangal joint (called podagra). Other joints also may be affected including tarsal joints, ankle and knee. The fingers joints may be inflamed in elderly patients.
   - Many attacks occur suddenly at night with rapid evolution of joints with erythema, swelling, tenderness and warmth. Intense joint inflammation can extend in to the soft tissue and mimic cellulitis or phlebitis. Fever can occur in sever attacks.
   - Polyarticular involvement can occur in some cases, and typically progression from monoarticular to polyarticular involvement occurs by extension to adjacent joints.
   - ***Course:*** acute attacks usually resolve spontaneously in few days 9 3-10 days), although some can extend over several weeks. The affected joint usually returns to normal between attacks and patients do not have residual symptoms until the next episode.

c) ***Intercritical gout:*** The third stage of gout is an asymptomatic period after the initial attack. Recurrence of new attacks may occur during this stage.
   - Recurrence of monoarticular attacks: about 7% of patients never experience a new attack of acute gouty arthritis after the first attack. However 62% experience a recurrence of gouty arthritis with in 1 yr.
   - Typically the patient is asymptomatic between attacks, but attacks become more frequent and abate more gradually if urate deposition remains untreated.
   - ***Diseases progression:*** Attacks tend to become polyarticular and more sever over time. Some patients develop a chronic inflammatory arthritis without asymptomatic intervals leading to a condition which may resemble rheumatoid arthritis.

d) ***Chronic tophaceous gout:*** develop in untreated patients and is the final stage of gout. The tophus is a collection of urate crystal masses surrounded by inflammatory cells and fibrosis.
   - Typical locations for tophaceous deposits are
     - o The pinna of the ear
     - o The surfaces of chronically involved joints and subchondral bone as well as extensor surface of the forearm, olecranon , and the intrapatellar and Achilles tendons

e) ***Renal complications***: may arise at any stage of gout, but nephrolithiasis is the only common clinical presentation of renal involvement. Proteinuria and impaired ability to concentrate urine related to urate deposition in the renal interstitium have been described in gout patients.

Diagnostic work up

A) ***Acute gouty arthritis*** ;
   - ***Laboratory findings***
     - ***(1) Serum uric acid*** value often is not helpful in the clinical diagnosis of acute gout. Serum uric acid concentration is normal in at least 10 % of patients at the time of an acute attack and an elevated serum uric acid is nonspecific for acute gout. It can be used to assess the effectiveness of hypouricemic therapy.
     - ***(2) Synovial fluid analysis***: The demonstration of urate crystals, especial intracellular crystals, in synovial fluid is diagnostic. Synovial fluid WBC of 10,000-60,000 /µl with predominant neutrophils are common in acute attacks.

B) Chronic tophaceous gout:

- ***Physical appearance***; tophi are firm movable and superficial located. If they ulcerate a chalky material extrudes.
- ***Radiologic findings***: tophaceous deposits appear as well defined large erosions (punched out erosions) of the sbchondral bone. These erosions are more common at the first Metatarso phalangal joint (MTP), and at the base of the heads of phalanges: however any joint area can be affected. Typically gouty erosions have an overhanging edge of subchondral new bone formation
- *Aspiration*: tophi can be aspirated an crystals can be demonstrated

Therapy

1) Asymptomatic hyperuricemia: no need for treatment, other than correction of the underlying causes.

2) Acute gouty arthritis : drug treatment of acute gouty arthritis is most effective when started early after the symptoms begin

a) Colchicine has anti-inflammatory effect, and if it is given early, it is effective in 85 % of patients.

Dose: Colchicine 0.6 mg is given every hr until the relief of symptoms or gastrointestinal toxicity occurs. It may also be given intravenously during acute attack in patients who cannot take PO medication.

b) NSAID: are used in high but quickly tapered dose. Drugs like Aspirin that affect uric acid clearance should be avoided.

Indomethacine: 25-50 mg PO TID,

Ibuprofen: 800 mg Po TID

Diclofenac: 25-50 mg PO TID

c) Corticosteroids:

Oral glucocorticoids: Prednisolone, 30-50 mg/day as the initial dose and tapered over 5-7 days.

Intraarticular injections of steroids can be used to treat acute gout of single joint, particularly when the use of other agents is contraindicated.

d) Drugs that alter serum uric acid concentration (e.g. allopurinol, probenicide) should be avoided during acute attack, because of lowering of serum uric acid

level induces the release of crystals in to joint space and prolong the acute attack.

3) ***Intercritical gout***: Prophylactic treatment with small dose of colchicines (0.6 mg once or 2X per day) or small doses of a NSAID can be used to prevent new attacks.

4) ***Chronic tophaceous gout*** : the aim of therapy is to control hyperuricemia(i.e. to reduce serum urate level to < 5 mg/dl)

   a) ***Uricosuric agents*** (E.g. probenicide, Sulfinpyrazone). This drugs facilitate the renal excretion of uric acid. It can be used in patients who excrete less than 700 mg of uric acid daily, who have normal renal function, and who have no history of urinary stones.

      Dose: Probenicide 200 mg PO Bid increased gradually as needed up to 2 gm

   b) ***Xanthine Oxide inhibitors:*** include allopurinol; this drug competitively inhibits xanthine oxidase. This drug is preferred in patients with urate excretion greater than 1000 mg/day, creatinin clearance < 30 ml/min, tophaceous gout or history of nephrolithiasis.

      Dose: 300 mg single morning dose initially and may be increased up to 800 mg if needed.

      Dosage is reduced in the presence of renal failure to avoid toxicity.

References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Gout, pages 2046-2050.

2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, Gout, pages 727-532.