LECTURE NOTES

For Health Officers

Internal Medicine

Editors
Getachew Tizazu, M.D..
Jimma University
Tadesse Anteneh, M.D., M.P.H.
Hawassa University

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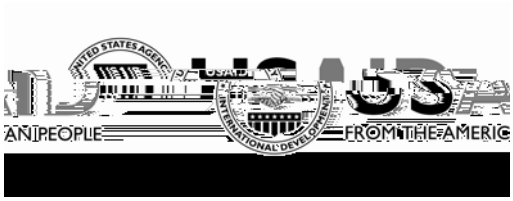
In collaboration with the Ethiopia Public Health Training Initiative, The Carter Center, the Ethiopia Ministry of Health, and the Ethiopia Ministry of Education



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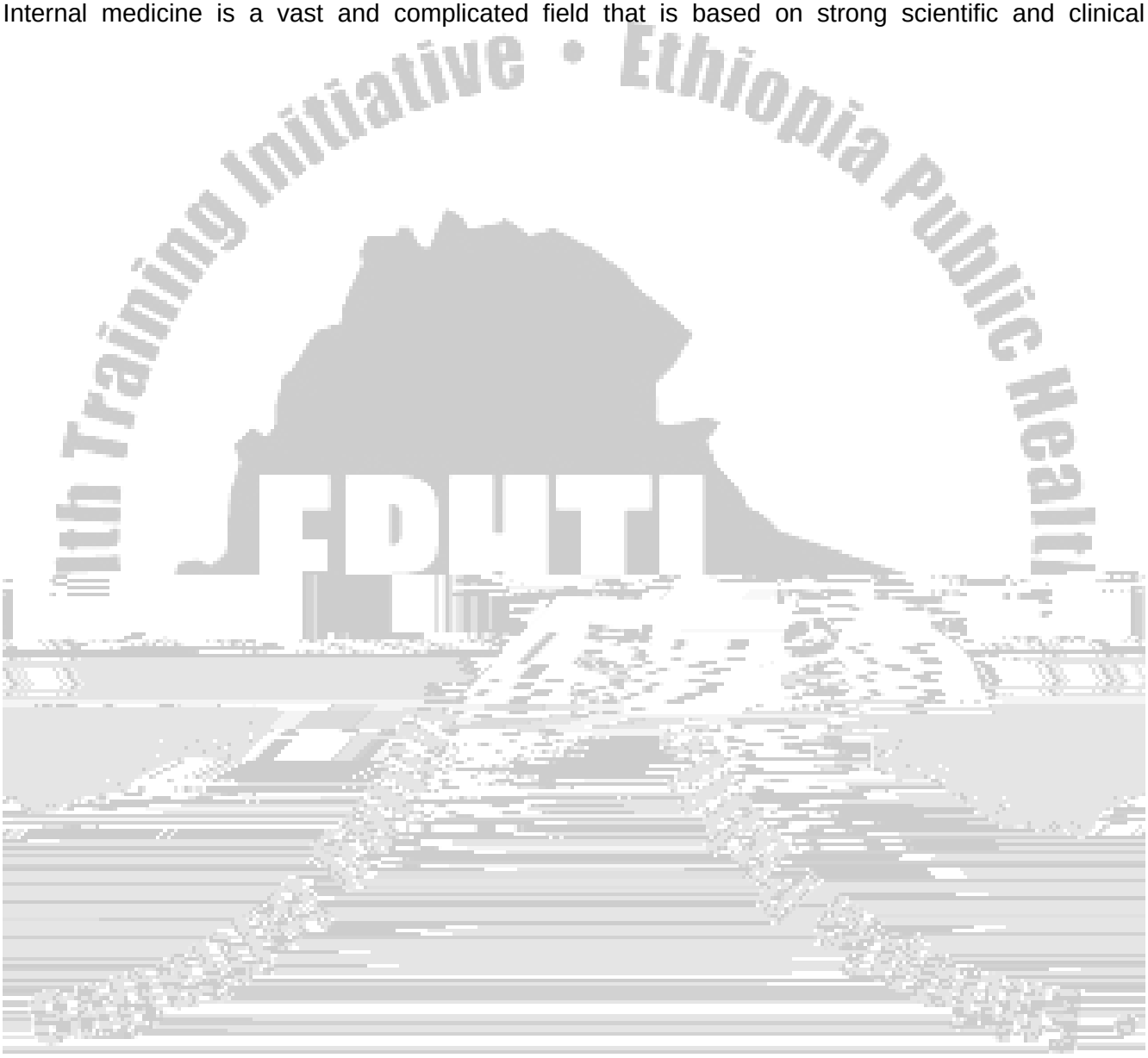
PREFACE

Internal medicine is a vast and complicated field that is based on strong scientific and clinical



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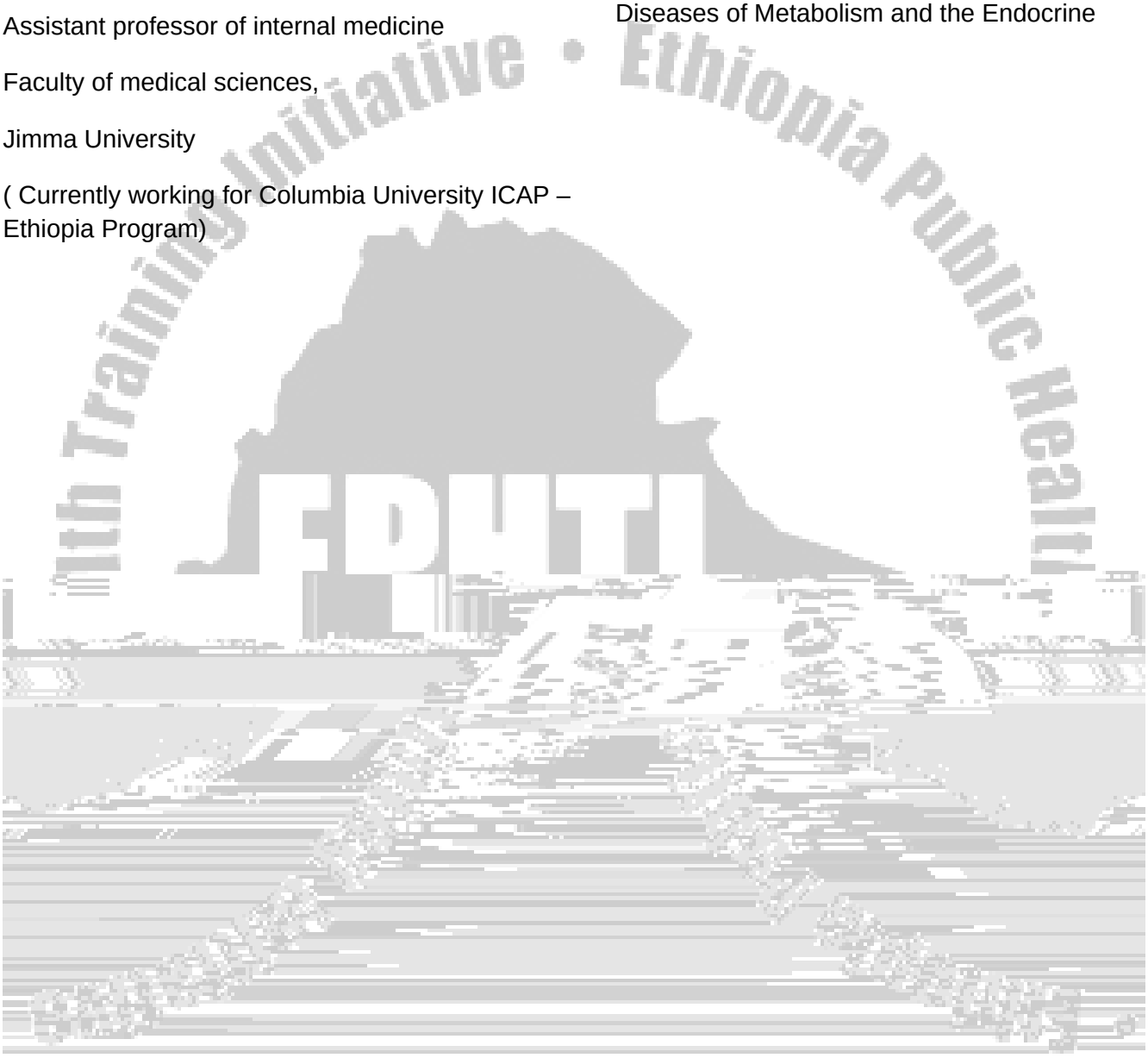
CONTRIBUTORS

Contributors	*Chapters or Topics contributed*
Getachew Tizazu, M.D. Assistant professor of internal medicine Faculty of medical sciences, Jimma University (Currently working for Columbia University ICAP – Ethiopia Program)	Infectious diseases Diseases of Metabolism and the Endocrine



Woldecherkos Abebe, M.D.

Assistant professor of Internal medicine ,

Faculty of Medical sciences ,

Jimma University

Diseases of the Cardiovascular System

Fetih Mohammed, M.D.

Assistant professor of Internal medicine ,

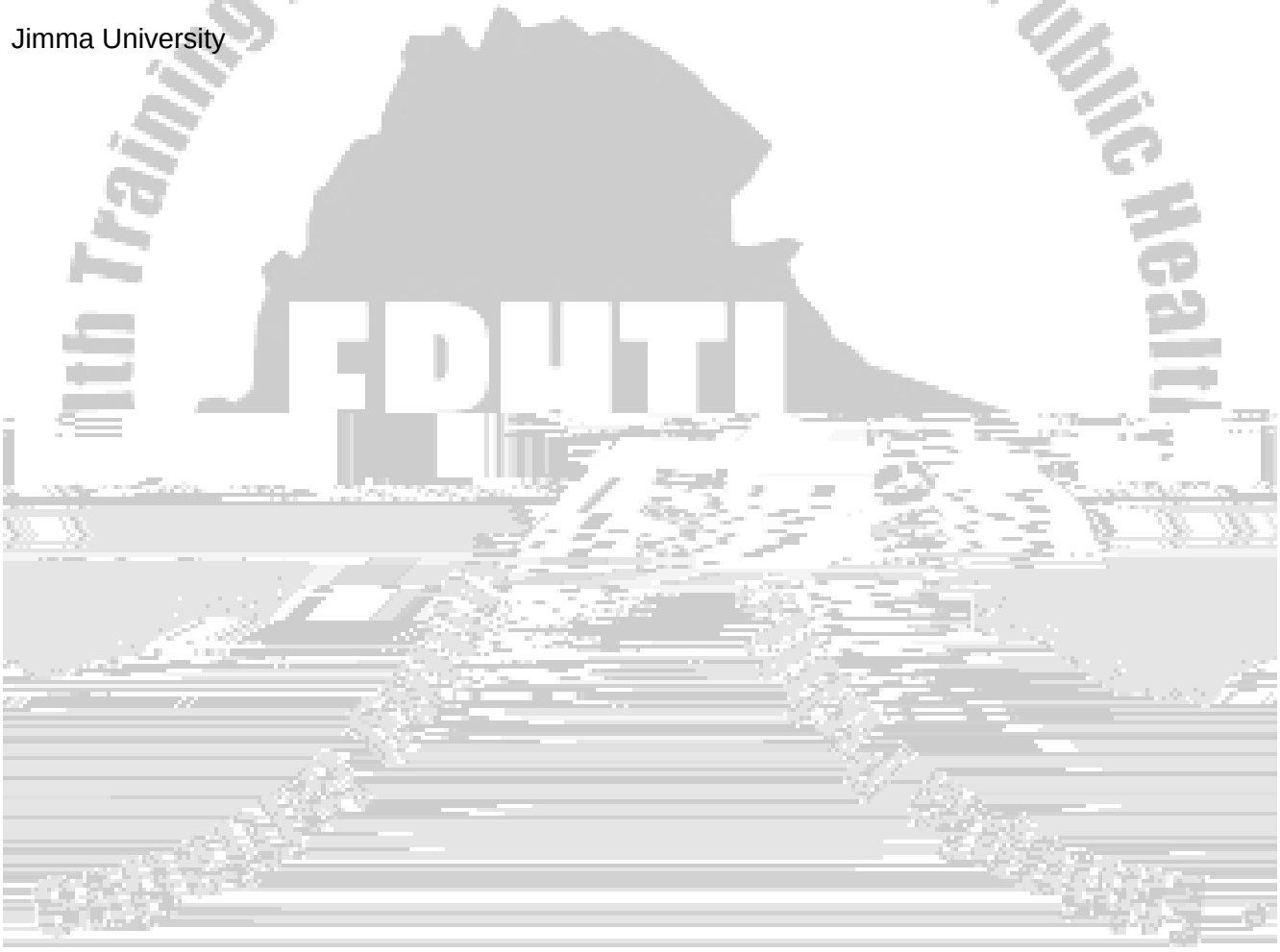
Health sciences Faculty,

Jimma University

Disease of the Respiratory System

Tuberculosis

HIV/AIDS **t3.un(ofs3k4ine ,)matologic d**



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LIST OF TABLES

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

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LH - Luetenizing hormone

LP – Lumbar puncture

LVH – left ventricular hypertrophy

MAC

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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;

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.

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.

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.

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.

:

Is first line of defense and serves to protect the host with out prior exposure to the infectious agent.

- : comprising T- lymphocytes, NK cells
- : comprises of B-Lymphocytes and antibodies produced by plasma cells.

Laboratory diagnosis

The lab diagnosis of infections requires the demonstration, either

1.

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*

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

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

- 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 - and H 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

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

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

- 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.

- 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 ( ) , 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.


Human
Human
Mosquito
Merozoites
H
A

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

Plasmodium malaria Pl. vivax / ovale (dormant hypnocytes may stay in liver and cause later relapse)	21 – 42 days 10 – 21 days	no fever for 2 days no fever for 1 day (both irregular at first)	no relapses relapses possible for up to 5 years
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 1.7v616ting is common.0 -1.7213 10.98 6s c-0.6s i924

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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.

(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*
-

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

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
  : 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
  : concentrates the parasite 20-40 times, this helps to determine parasite concentration.

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

- 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):

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

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

(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.

- is most widely used in Ethiopia.

Tablet containing 20 mg Artemether plus 120 mg Lumefantrine in a fixed dose combination.

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

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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.

2.4 mg/kg IV or IM stat followed by 1.2 mg/kg at 12 and 24 hrs and then daily.

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

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

- Huge spleen (> 10 cm BLLCM) with or with out hepatomegaly
- Hyperspleenism (anaemia, pancytopenia)
- Marked elevation of serum

- 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

- 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

- 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

- 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.

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- 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

- 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.

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,

2.2 Typhoid (Enteric) Fever

: 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*

Typhoid fever is a systemic infection characterized by fever and abdominal pain caused by dissemination of Salmonella typhi

Salmonellae disseminate throughout the body in macrophages via lymphatic and colonize reticuloendothilial tissue (liver, spleen, lymph nodes, and bone marrow). Patients have relatively

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- Leucopenia

But definitive diagnosis of the disease requires laboratory tests.

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;
- -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.
- is negative in the first week and becomes positive in 75% of patients in the 3rd week. Urine culture parallels stool culture.

- 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.

- 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.

- 500mg PO BID for 10 days
- 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

- 1 gm PO daily for 5 days
- 500 mg Po QID for 14 days
- 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.

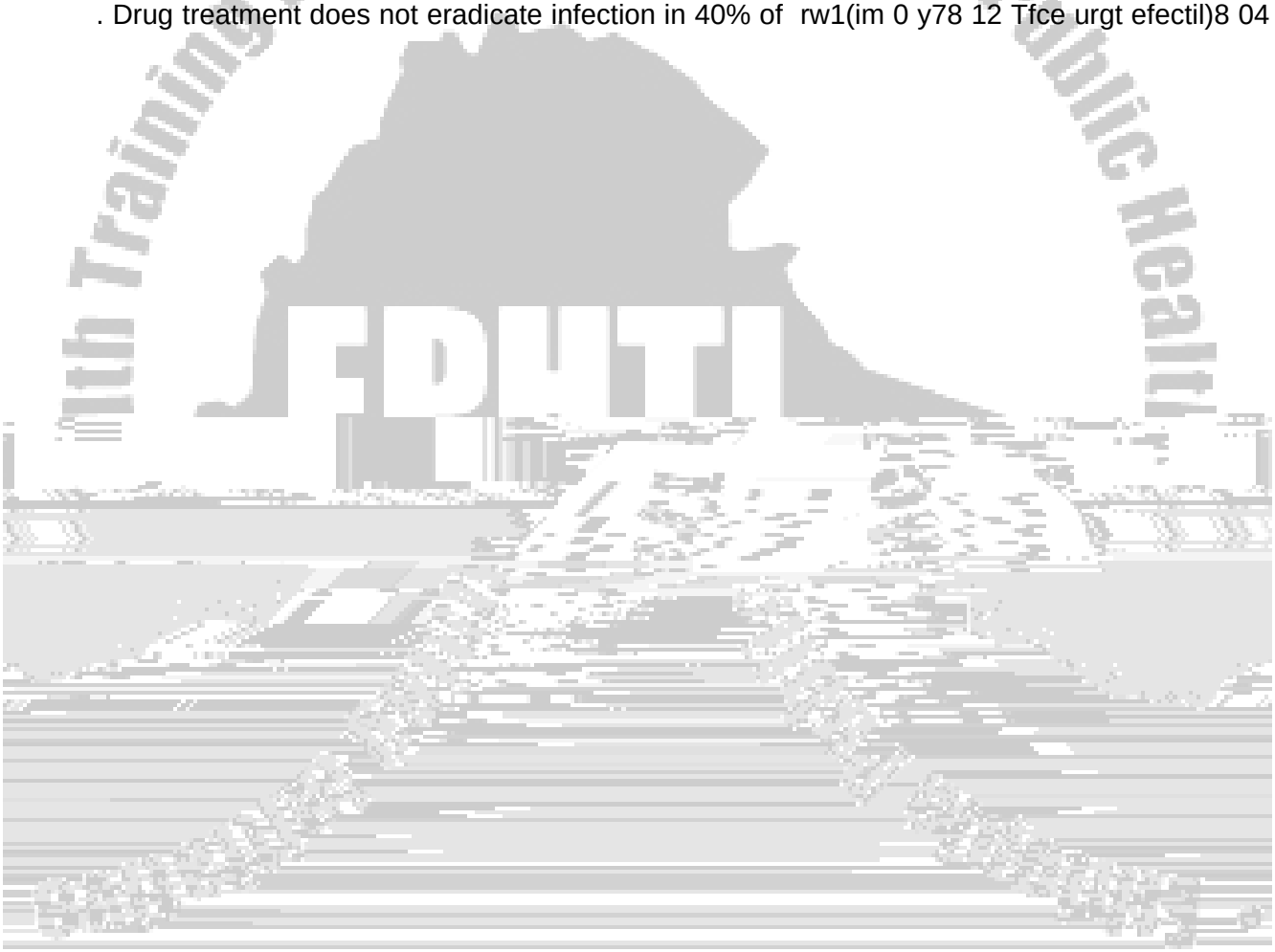
Intravenous drugs are recommended for critically sick patients who are admiited or for patients who are unable to take oral drugs

- 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).

- 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.
- 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..

. Drug treatment does not eradicate infection in 40% of rw1(im 0 y78 12 Tfce urgt efectil)8 04 6 20.8197 -



2.3 Relapsing Fever

: 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*

:

: 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)

- 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.

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,

- 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.

• Erythromycin	500mg	500mg every 6 hrs
• Tetracycline	500mg	500mg every 6 hrs
• Doxycycline	100mg	100mg every 12 hrs
• Chloramphenicol	500mg	500mg every 6 hrs
Penicillin G (procaine)	600,000 I.M stat	600,000 IM daily

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

- 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 singl slase creatm5.5(munt owih edoxyc-763(iyclne))]TJ/TT9 1 Tf-0.45

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2.4 Rickettisial diseases: (

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

1. *Define rickettsial diseases with Special Emphasis on Epidemic and Endemic Typhus*

Etiology and Epidemiology of Epidemic and Endemic Typhus

: 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.

is cause by ***R. thyphi*** which is transmitted by fleas. *R.typhi*

- Tongue may be dry, brown, f6-hred

Laboratory investigations*;*

:

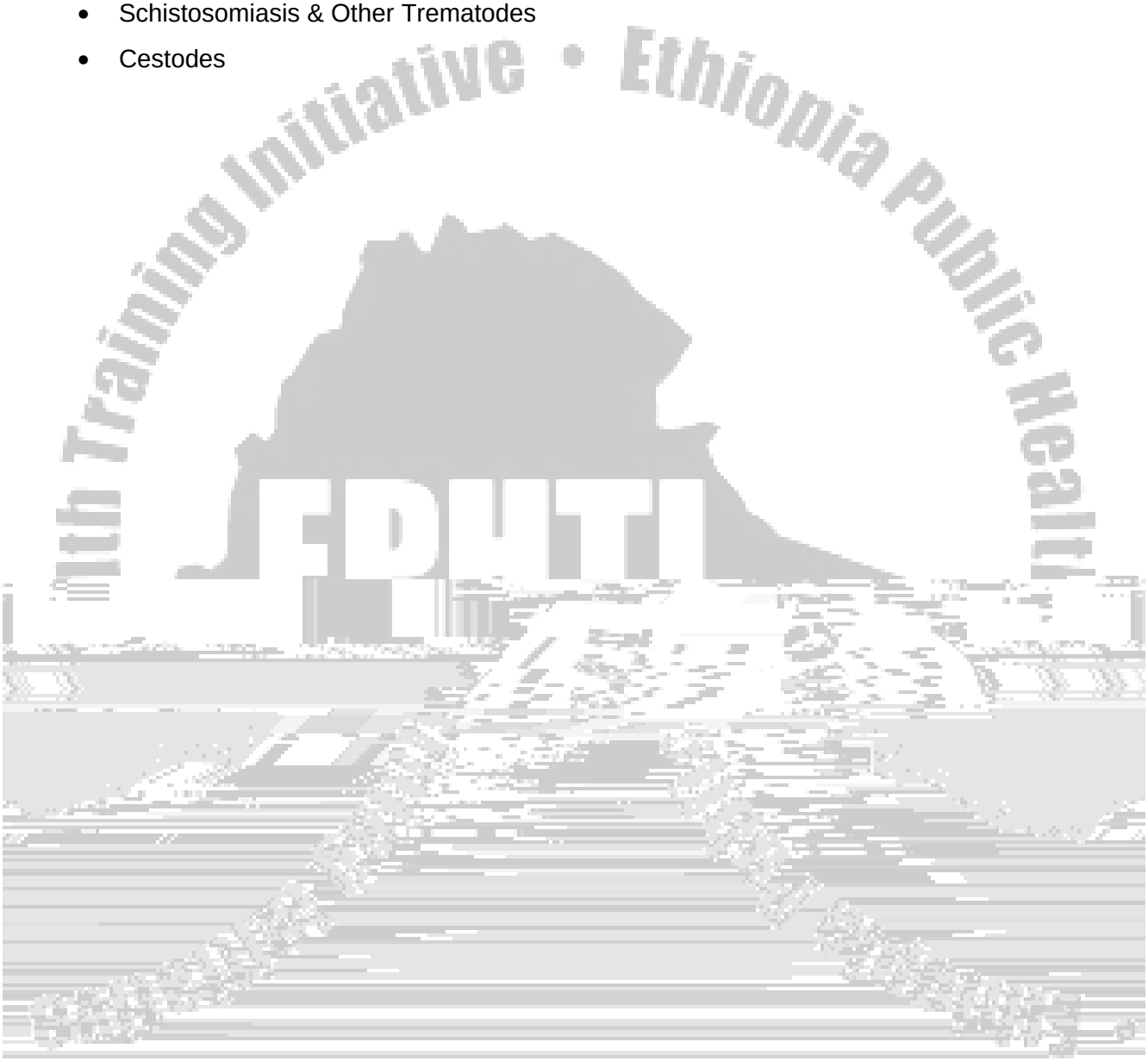
- Indirect fluorescent antibody test
- : This is widely used by many of the hospitals and the private clinics in this country, is not specific or sensitive.

into laboratory animals is possible, it is time

- Wash the patient with soap and water & apply insecticides all over & disinfect clothing

3. Helminthic Infections

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



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.

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

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

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

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- 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.

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.

Even asymptomatic patients should be treated.

- , 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.
- 200µg/kg as a single dose daily for 1 or 2 days is better tolerated. Disseminated cases should be treated for 5-7 days.
- 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)

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

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

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

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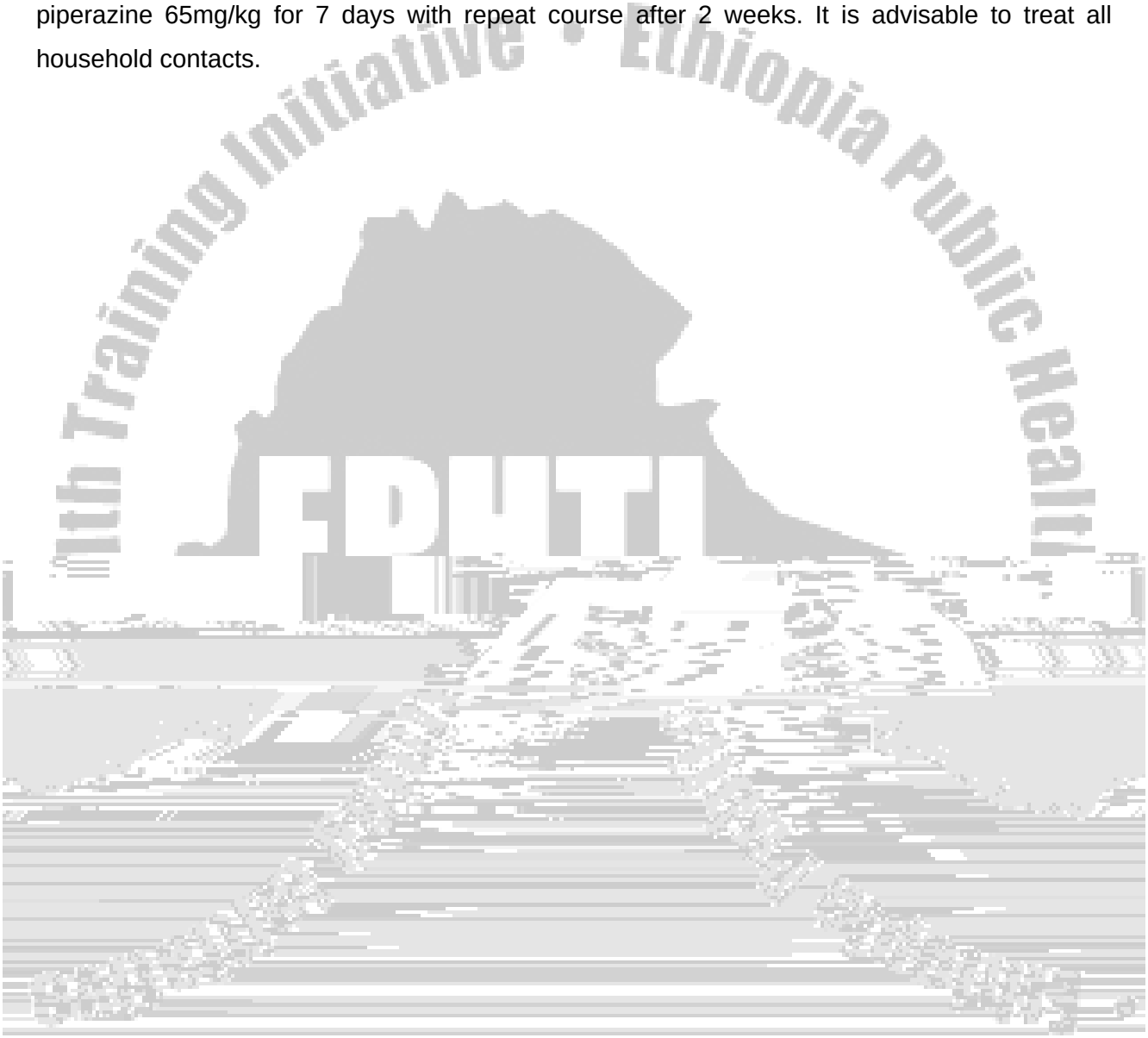
cellulose tape to the perianal region in the morning. The tape is then transferred to slide to be seen under a microscope.

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.



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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.

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.

Current antihelminthics are not effective. Most lightly infected patients recover with bed rest, antipyretics and analgesics. Thiabendaz39.s

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.

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.

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

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

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

Infection in humans begins with deposition infective larvae on the skin by the

- 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

- 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)

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.

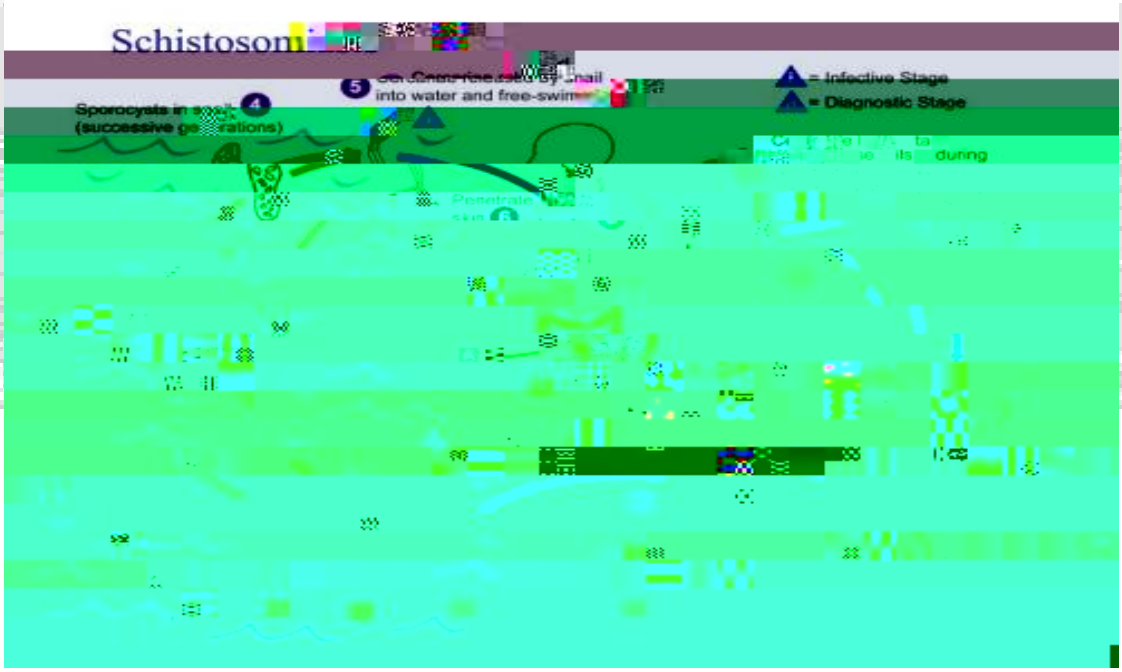
Life cycle

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



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:-

. : 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 . It is seen in new comers and not common in indigenous people.

(also called toxemia stage/ 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.

( ) 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.

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

: 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, heavi(o)af of ed5(nutioi4).4(mnitiv7(.of cest)5Cestode0 Tc0 T9.459 0o580.0013 Et the epid7m)91 aMe t

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3.6 Leishmaniasis

: 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*

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

Classification of leishmaniasis

There are three major clinical forms of 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

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

Management

Patients need hospitalization for proper treatment and follow up.

-

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

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	Hyr	Spontaneous healing with

- 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

- - by surgery, curettage, cryotherapy or hyperthermia (40-42^{0}c) or
- 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.
-

References:

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

- 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.

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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).

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.
- may reveal a chronically sick patient with pallor and clubbing. Inspiratory crepitations are seen in some cases.

-

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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.
- 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 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.

  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.

- 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.
- 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.
- is a very important clue for the diagnosis even though this is nonspecific. There could also be anemia of chronic illness.
- test is widely used to screen tuberculosis in developed countries where the

- A patient in whom TB has been bacteriologically confirmed or diagnosed by a clinician.
-

Anti Tuberculosis Chemotherapy

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

- : 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.
- 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.

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

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

		Burning Sensation in the Feet (Peripheral neuropathy)	Pyridoxine 100 mg PO daily
		Jaundice /Hepatitis	Stop INH
		Orange or red discoloration of urine Nausea , abdominal pain	Reassurance Take drug with small meal
		Hepatitis , Acute renal failure shock , purpura	Stop Rifampcin
	Ethambutol	None	
		Major	

- 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

5. Human Immuno Deficiency Virus – HIV/AIDS

: 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

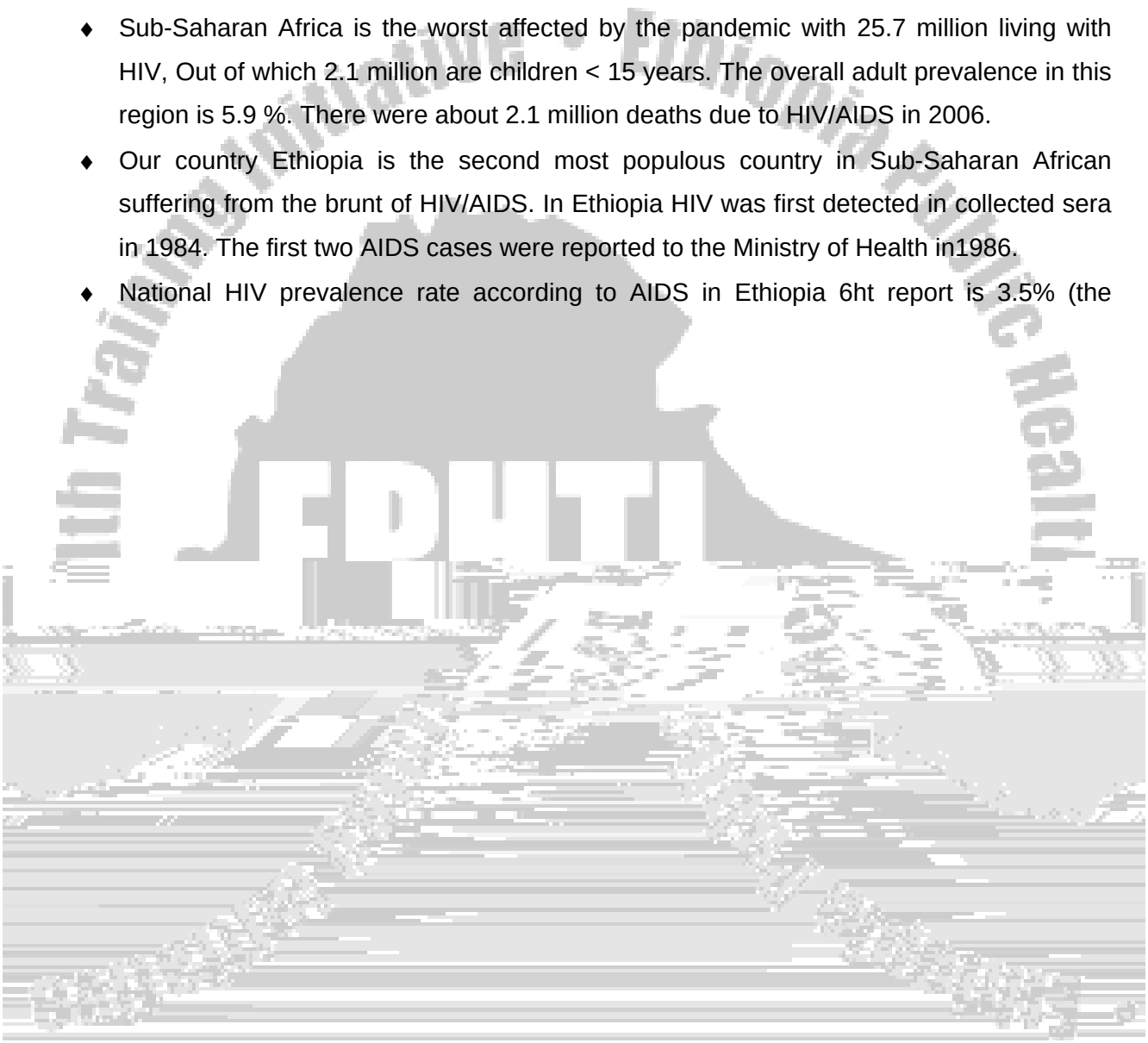
Kaposi's sarcoma was diagnosed in 26 homosexuals with

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



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 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

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

Premature delivery
Immature immune status
First-born twin

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

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

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

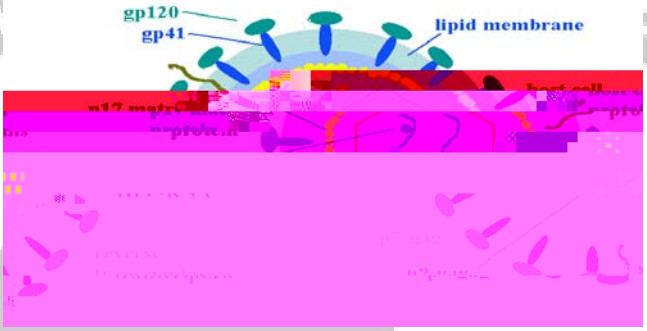
- : relatively rare seen in Cameron and Gambia

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

- 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.

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)

  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

  - HIV-mediated direct cytopathicity (single cell killing) – infected 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
-

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

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

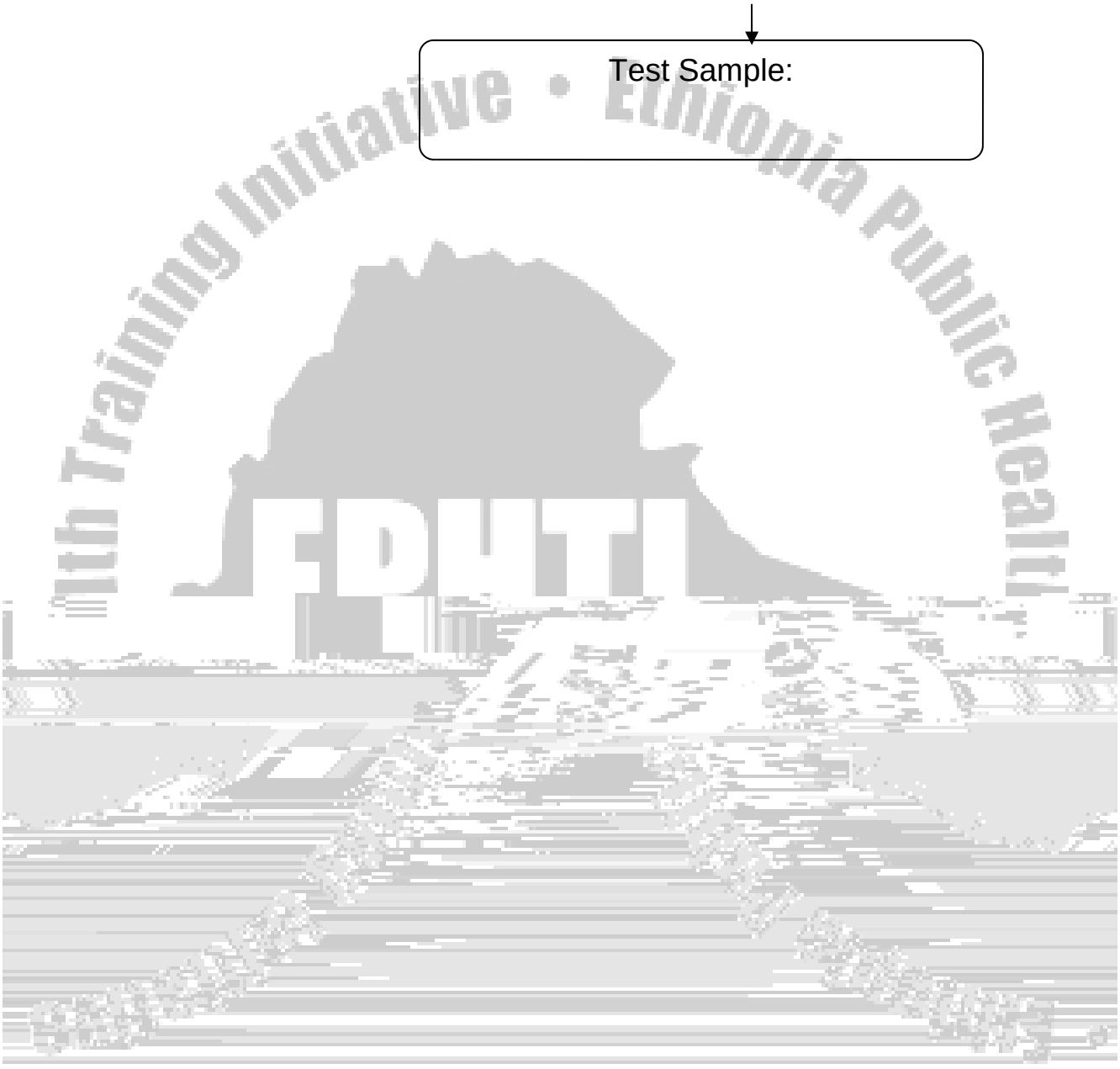
After the initial primary infection patients remain health for 6- 8 years before they start having overt clinical manifestations: account for 80 % of all patients

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.

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

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

o



- 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.

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

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

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

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

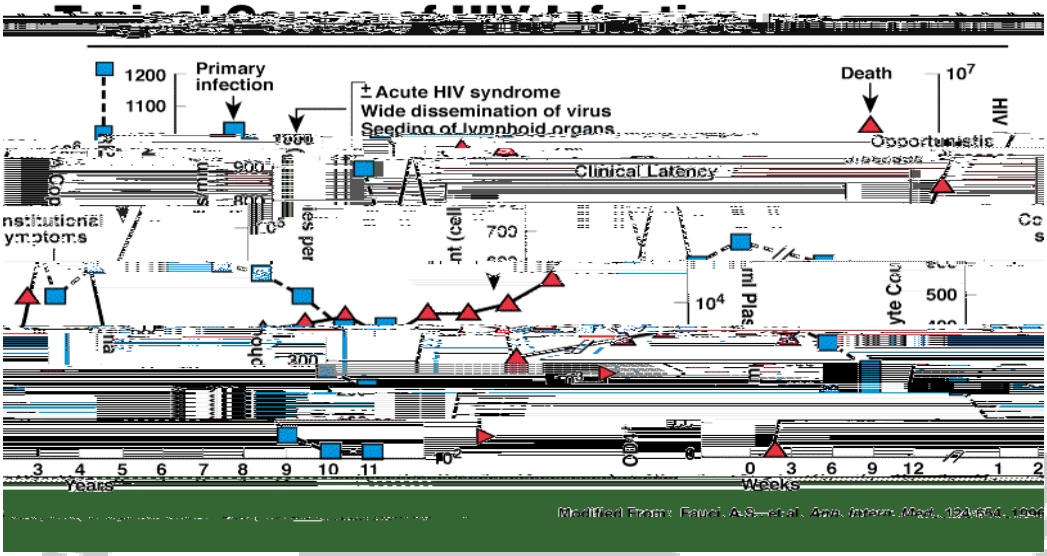
Malaria blood slide

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,
  -

- 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:

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

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

  - o 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
  - o When it involves the esophagus, patients complain of difficulty and/or pain on swallowing
  - o Is due to Candida infection
  - o Confirmatory diagnosis is by direct examination of a scraping for pseudohyphal elements
  - o - 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.

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

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

- 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%

- 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

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

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

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

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.

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

- 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.

♦ :

- 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)

- ***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

  : Prednisone 40 mg PO bid x 5 days

  40 mg daily for 5 days

  20 mg daily for 11 days

PCP - preventive therapies

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

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

♦ HIV associated thrush

♦ Unexplained fever

is indicated for patients with prior episode of PCP

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

- ♦ 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.

- ♦ 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 %

Clinical Presentation depends on degree of immunosupression

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

	Early stage of HIV Infection	***Late stage of HIV Infection***
Clinical Presentation	Similar to non HIV infected with productive cough Pulmonary manifestations dominate	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 TB in HIV)

- 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.

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

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

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

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

- Primary CNS Lymphoma

- 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)

  lymphocyte pleocytosis 10-100 cells/ l
  - Increased protein level protein< 100mg/dl,
  - Normal glucose level

The syndrome usually resolves spontaneously within 2-4 weeks.

: 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

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.

Ethiopia Public Health Training Initiative
FPHTI

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

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

- 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

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/ l

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%
- 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-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

	Inability to Concentrate	Altered personality	
	Mental Slowing Forgetfulness	Social withdrawal	Poor coordination
	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

Mono neuropathy e.g. Bell's palsy

Mononuritis multiplex

Distal sensory peripheral polyneuropathy (DSPN)

Is the most common.

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

Erythematous Form : there is predominantly erythema rather that white patches

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

Mechanism of diarrhea

Adhesion to mucosal surface

Treatment

Hydration: oral , parentaral with electrolyte replacement

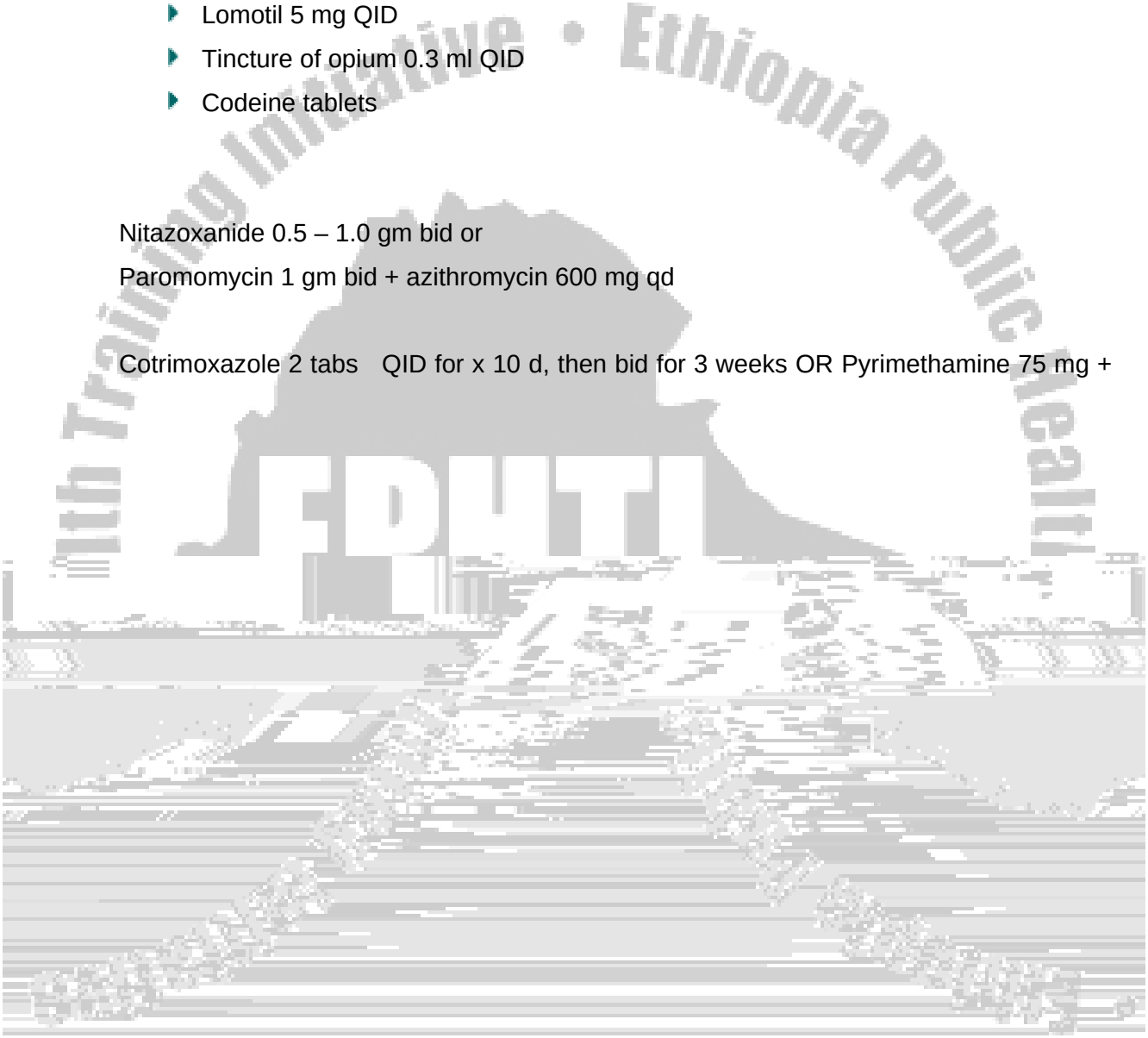
Symptomatic treatment : Anti-diarrheal agents

- Loperamide 2-4 mg QID
- Lomotil 5 mg QID
- Tincture of opium 0.3 ml QID
- Codeine tablets

Nitazoxanide 0.5 – 1.0 gm bid or

Paromomycin 1 gm bid + azithromycin 600 mg qd

Cotrimoxazole 2 tabs QID for x 10 d, then bid for 3 weeks OR Pyrimethamine 75 mg +



- CNS , peritoneum and liver may also be invaded

Severe systemic symptoms are commonly seen in disseminated infections

May be complicated by Gram negative sepsis

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

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

- 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

- 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
-
    - 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

- 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

: Antipruritic lotion, Corticostroid, Oatmeal bath

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

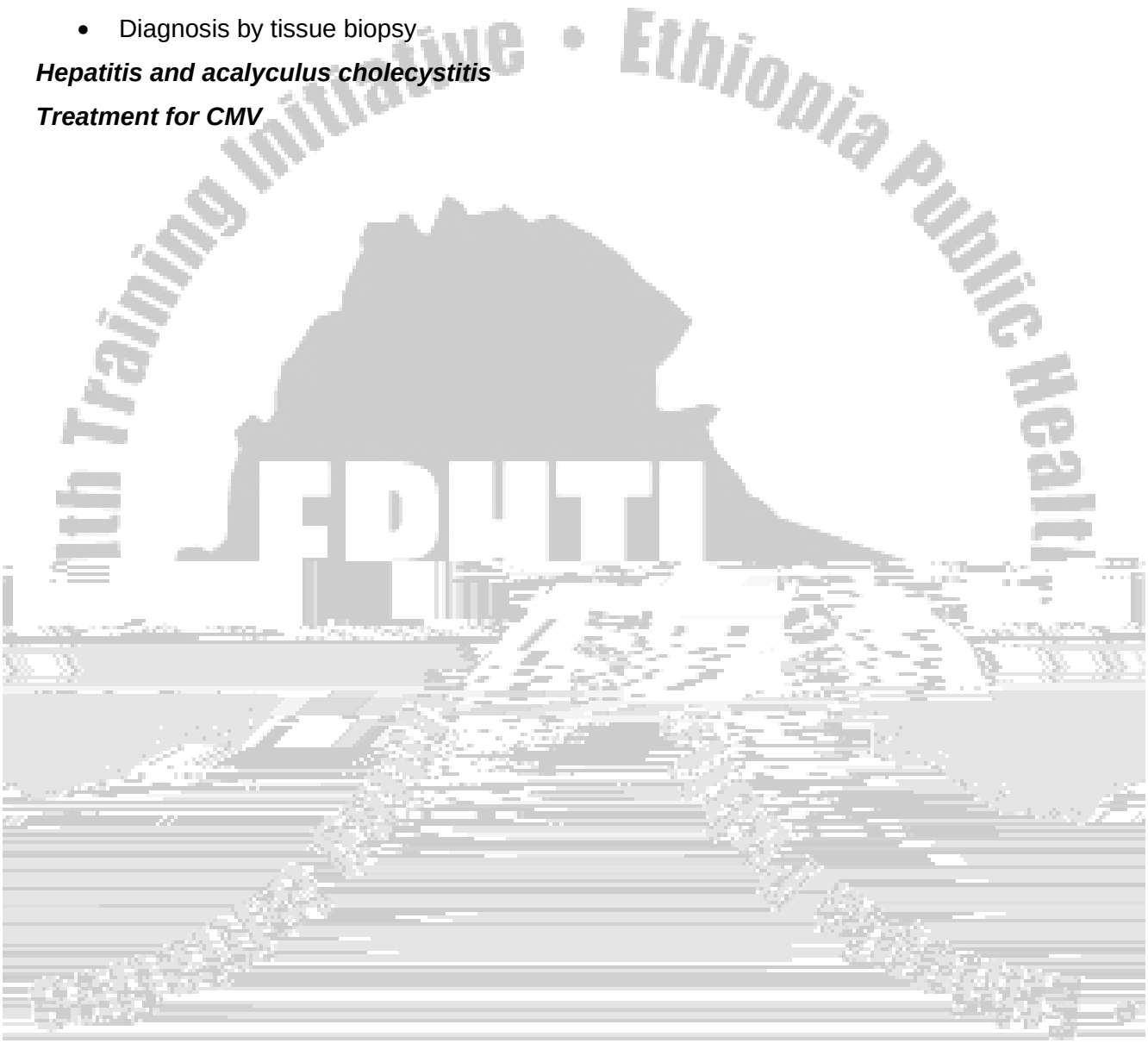
- Pain and difficulty in swallowing
- Diagnosis by tissue biopsy

Colitis

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

Hepatitis and acalyculus cholecystitis

Treatment for CMV



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

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

- Alitretinoin gel (35-50% response),Local radiation (20-70% response)
-

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

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

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***		

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

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- : 1 x 300mg tablet BID
- 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* actually, a nucleoTIDE

1 x 300mg tablet QD

: Headache, Nausea, Diarrhea, Lactic acidosis

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

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*.

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

Didanosine (ddI) (2)

Food Interactions: take on empty stomach

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

2) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

-
-

- ***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

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

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

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

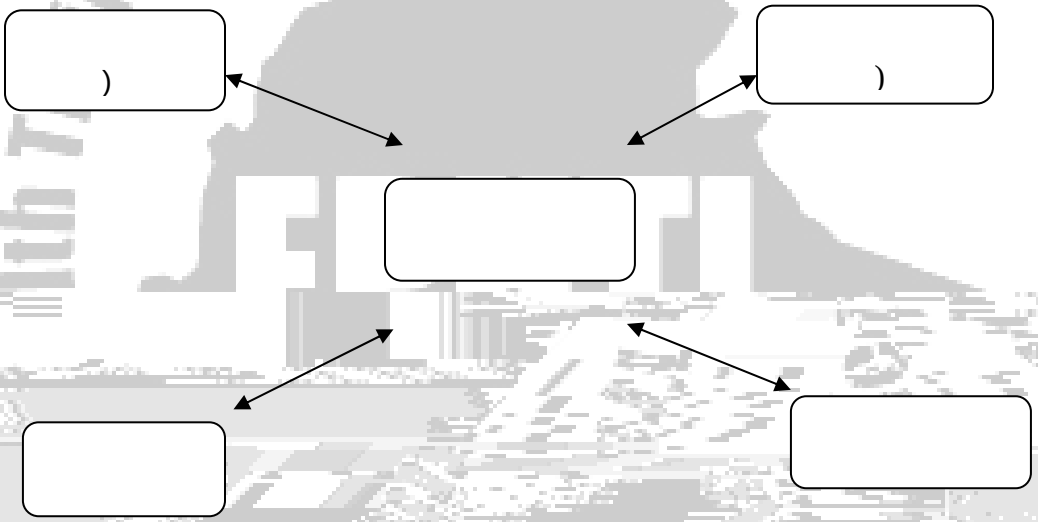
WHO Criteria to Initiate ART in Adults and adolescents

WHO clinical stage	***CD4 testing not available***	***CD4 testing available***

- Oral candidiasis

- 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

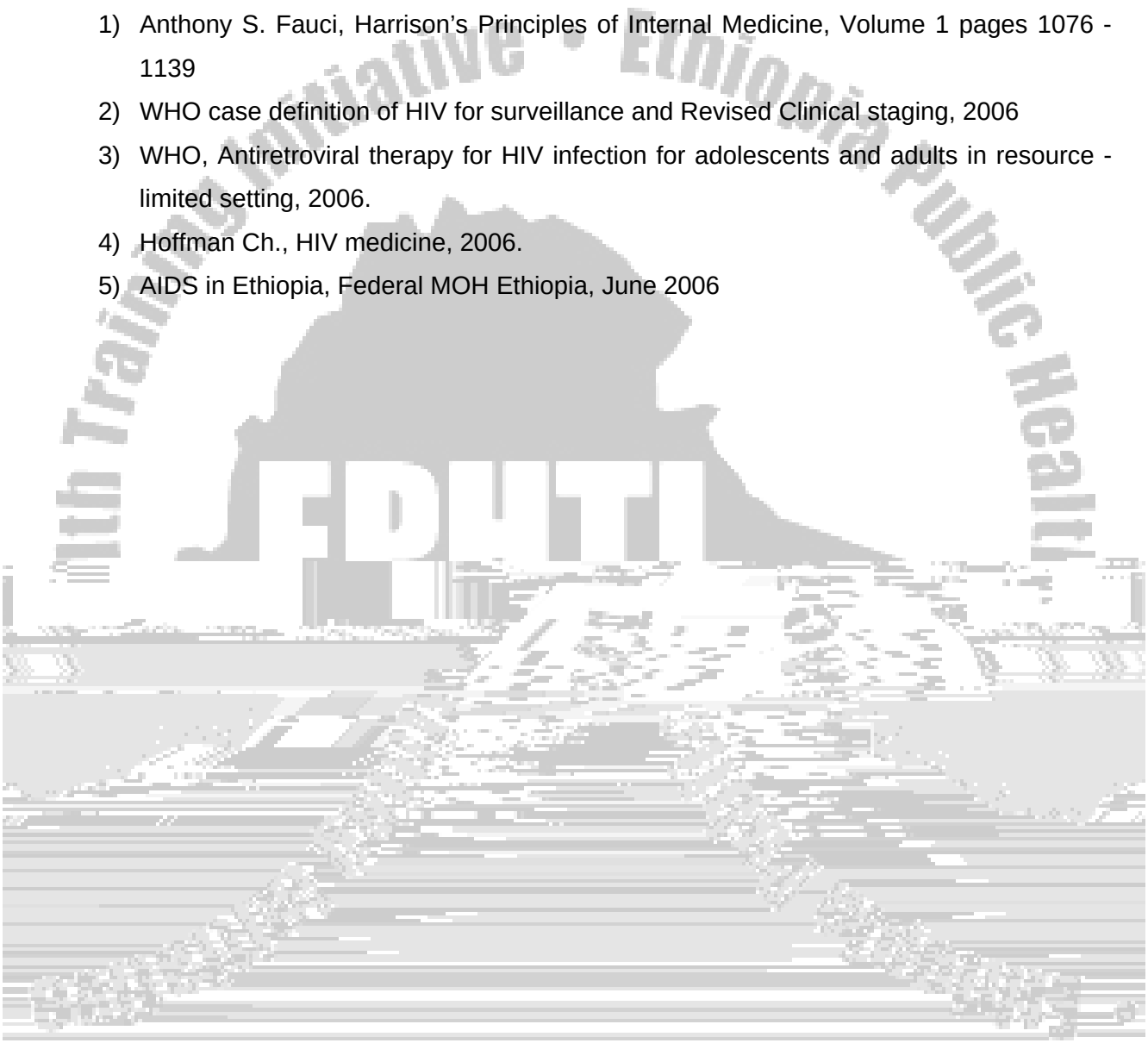
ABC or TDF or ZDV (if not taken)/+ Didianosin (ddI) + Kaletra® LPV/r or SQV/r or NFV

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

References:

1) Anthony S. Fauci, Harrison's Principles of Internal Medicine, Volume 1 pages 1076 - 1139
2) WHO case definition of HIV for surveillance and Revised Clinical staging, 2006
3) WHO, Antiretroviral therapy for HIV infection for adolescents and adults in resource - limited setting, 2006.
4) Hoffman Ch., HIV medicine, 2006.
5) AIDS in Ethiopia, Federal MOH Ethiopia, June 2006



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

- :

  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.*

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- 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.

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

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 Spectinomycin 2gm IM stat Doxycycline 100 mg PO BID for 7 days 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.

- *Treponema pallidum (syphilis)*
- *Haemophilus ducreyi (chancroid)*
- *Calymmatobacterium granulomatis (granuloma inguinale)*
- *C.trachomatis serovar L_1-L_3*

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

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- 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

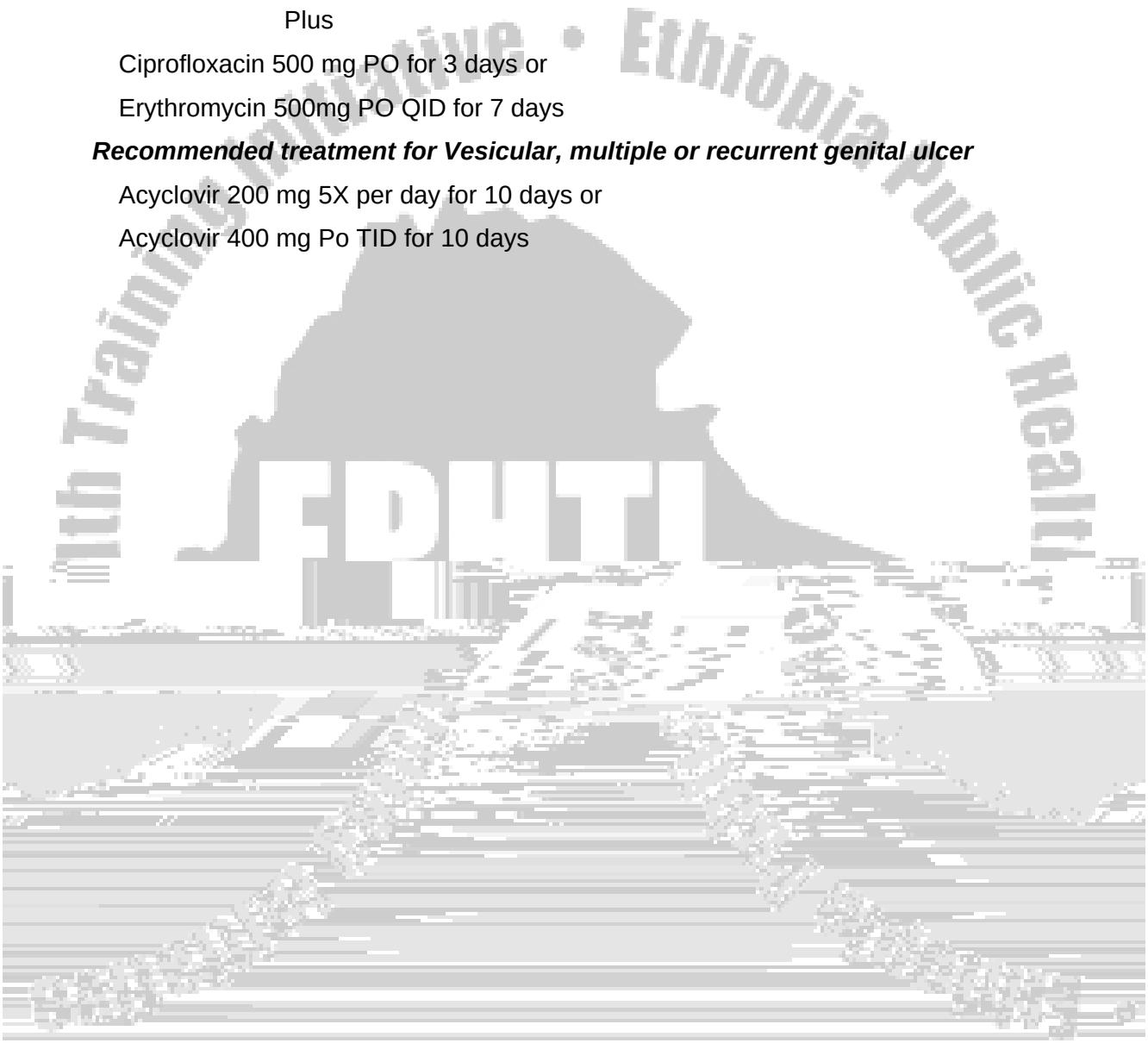
Ciprofloxacin 500 mg PO for 3 days or

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



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:

-

- 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 Spectinomycin 2gm IM stat Doxycycline 100 mg PO BID for 14 days 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*

- *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 transmi.3(aalgesSynr 72 649.5601)Tj0 -1.7322 TD

7. Other Important Infectious Diseases

7.1. Tetanus

: 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.*

- *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

:

- 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.
- 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

- Human tetanus immune globulin (TIG) is the choice and if available should be given early.
-

7.2. Rabies

: 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

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

7.3. Anthrax

: 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.

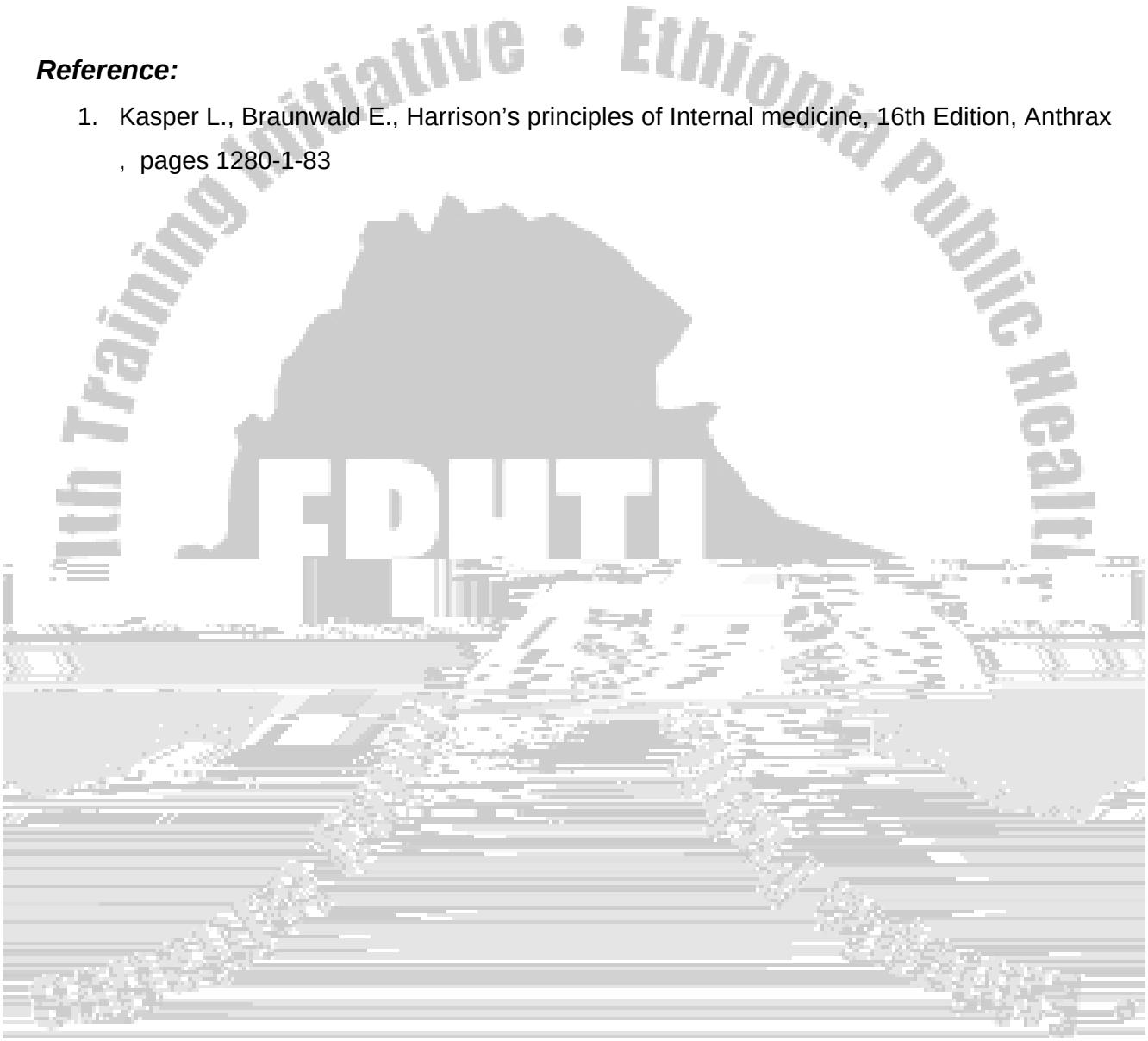
Gastrointestinal anthrax:

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



6.4 Brucellosis

: 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.

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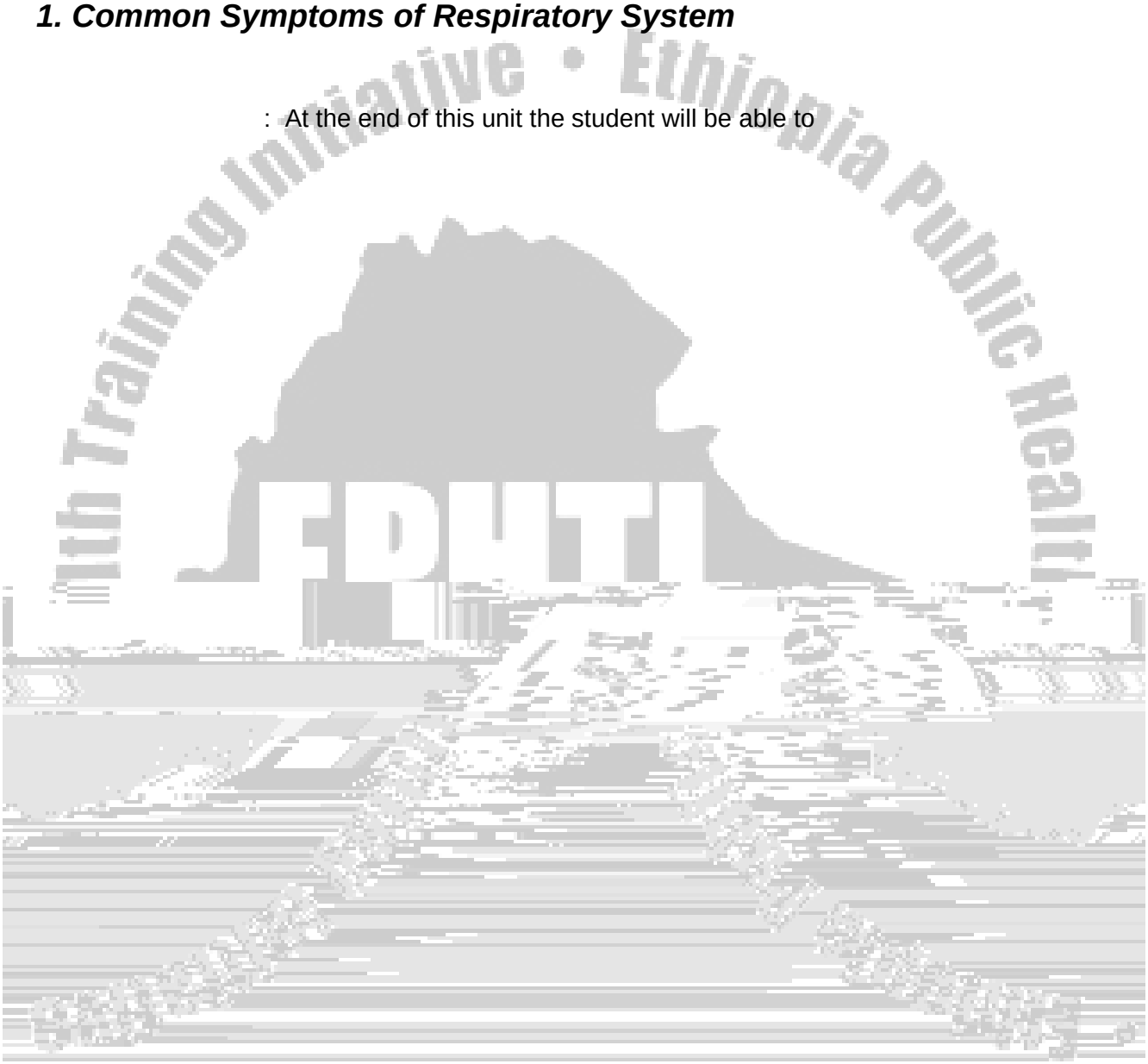
1. Common Symptoms of Respiratory System

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



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.

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.

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Approach to the patient with hemoptysis

2. Upper Respiratory Tract Infections

: 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 1^{st} or 2^{nd} day of symptoms, become more mucous and purulent. Hacking cough associated with scanty sputum often lasts into the 2^{nd} 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.

- 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.

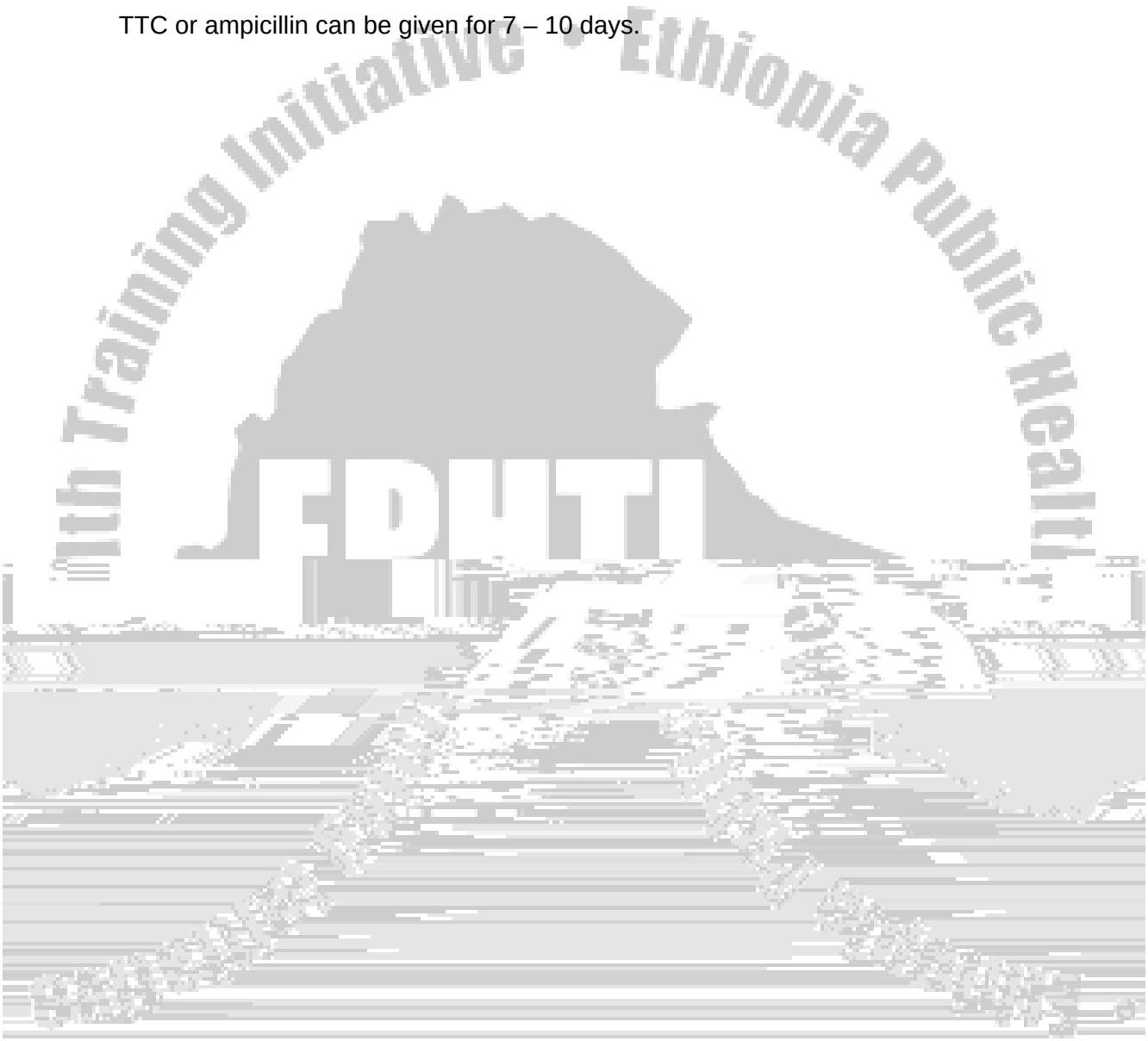
Diagnosis:

- 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.



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

- 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

- 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.

- 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

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 orx

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

4. Bronchial Asthma

Table II-4-1 Comparison of the two major types of Asthma

	Allergic (Atopic) asthma	***Non Allergic (idiosyncratic)***

- ***Exercise: is*** a very common precipitant of acute episodes of asthma
- 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.
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- 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

Differential diagnosis includes:

- : foreign body obstruction, viral URTI involving the epiglottis (croup), and bronchiolitis (RSV infection);
- : 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.

- 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

- 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

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	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,

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.

- 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 hyperinflati

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

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

6. Suppurative lung diseases

6.1 Bronchiectasis

: 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

6.2 Lung abscess

demonstrating parenchymal infiltrates with cavity

Pleurisy and Pleural Effusion

- Pancreatitis
- Uremic pleural effusion
-

- 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

: 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

- - 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 (occupational) or
- Exposures to other carcinogens :Ni, Co, Cr, Asbestos, Polycyclic aromatic hydrocarbons, Silica , Mustard gas (world war I)

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%

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- Central or peripheral locations
- Metastasizes very rapidly and widely

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).
-

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.

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

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

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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1. Rheumatic Fever

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*

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.

- 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 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
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 & 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

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

2. Congestive Heart Failure

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

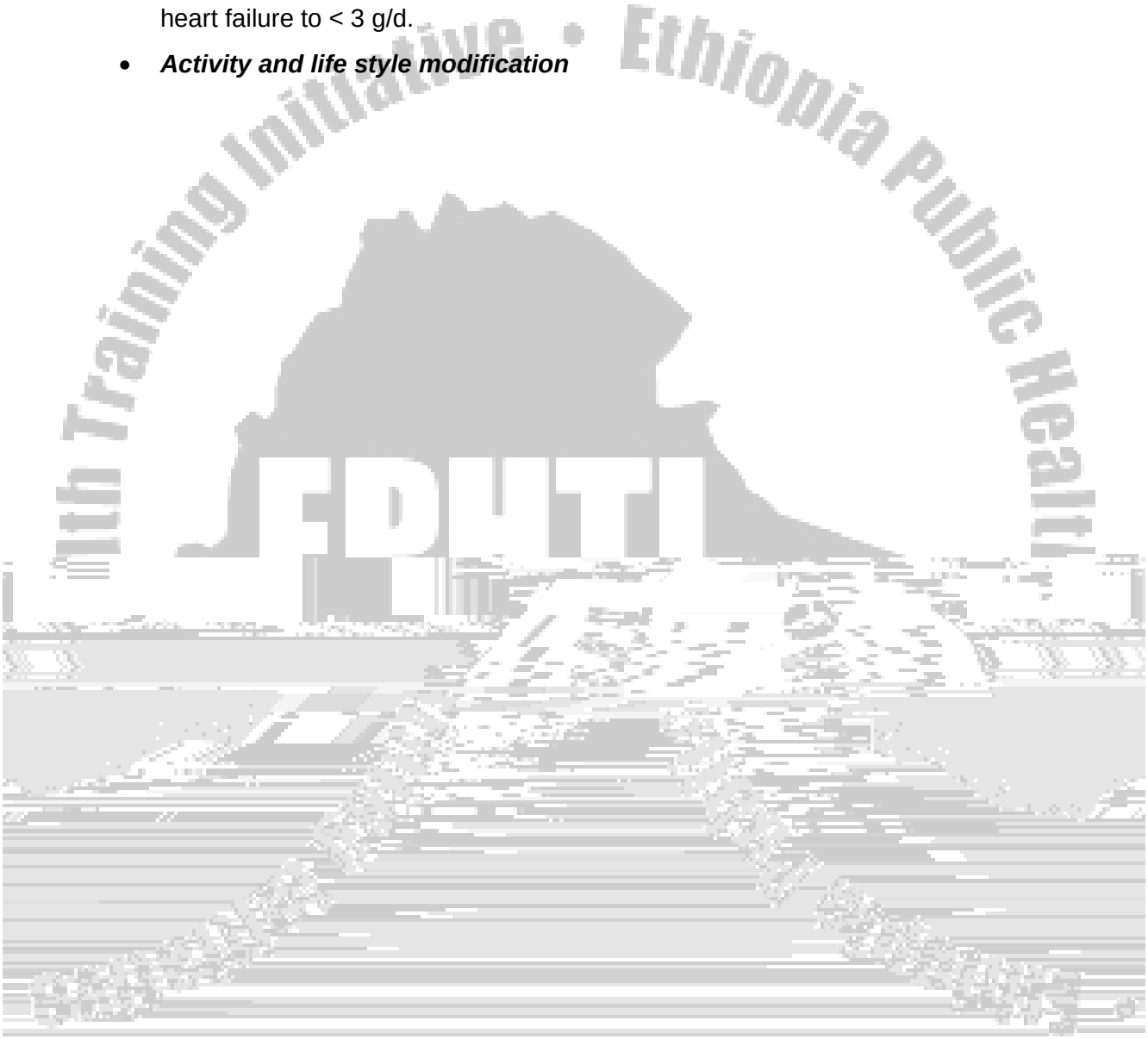
- Progressive dyspnea which initially occurs with exertion and later occurs at rest. Dyspnea on exertion has been found to be the most sensitive complaint, yet the specificity for dyspnea is less than 60%.
- Orthopnea and paroxysmal nocturnal dyspnea (PND) are more specific symptoms; however, sensitivity 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

- 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
-

4. *Prevention of deterioration of myocardial function (slowing progression of heart failure)*
5. *Treat the underlying cause*

- ***Dietary sodium restriction*** should be implemented in all patients with congestive heart failure to < 3 g/d.
- ***Activity and life style modification***



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.

x

- Electrolyte on toxicity is suspected, digoxin should be withheld, and has observe for some days before reinitiate with a lower dose. One should mp6d

- Creatinine > 265 mol/L (3mg/dl)

N.B The first two side effects are serious and necessitate immediate cessation of the drug.

2)

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)

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.

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.

3. Valvular Heart Diseases (VHD)

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 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.

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

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
-

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

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 enl

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.

- 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.

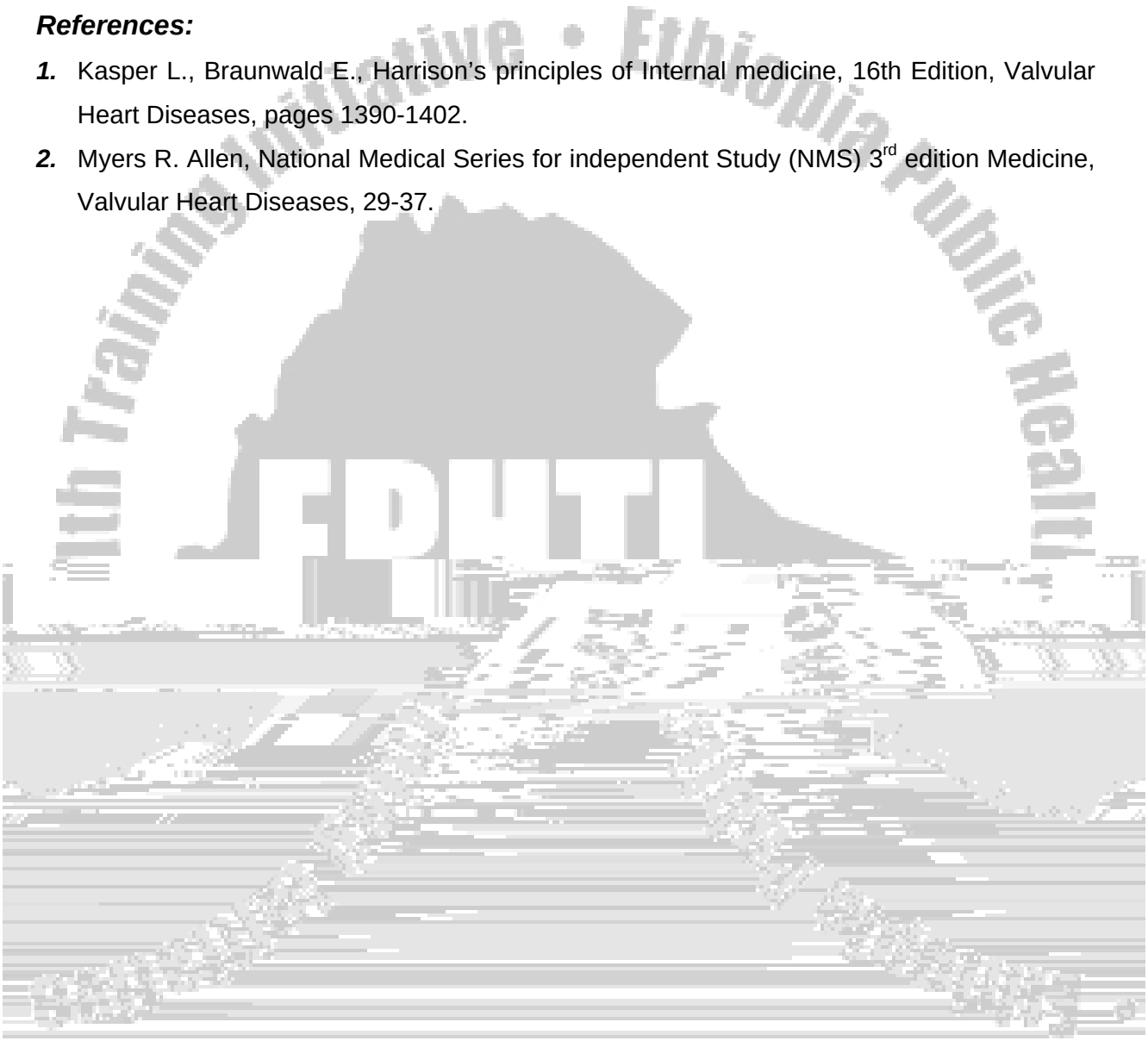
- Although the prevalence of mitral valve prolapse was once thought to be as high as 15

- 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.



4. Infective Endocarditis

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.
- 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

- 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;*

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:

- o Acute glomerulonephritis
- o Osler's nodes
- o Roth spots
- o 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 ofes) inrity 0324 6(n
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- 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.
-

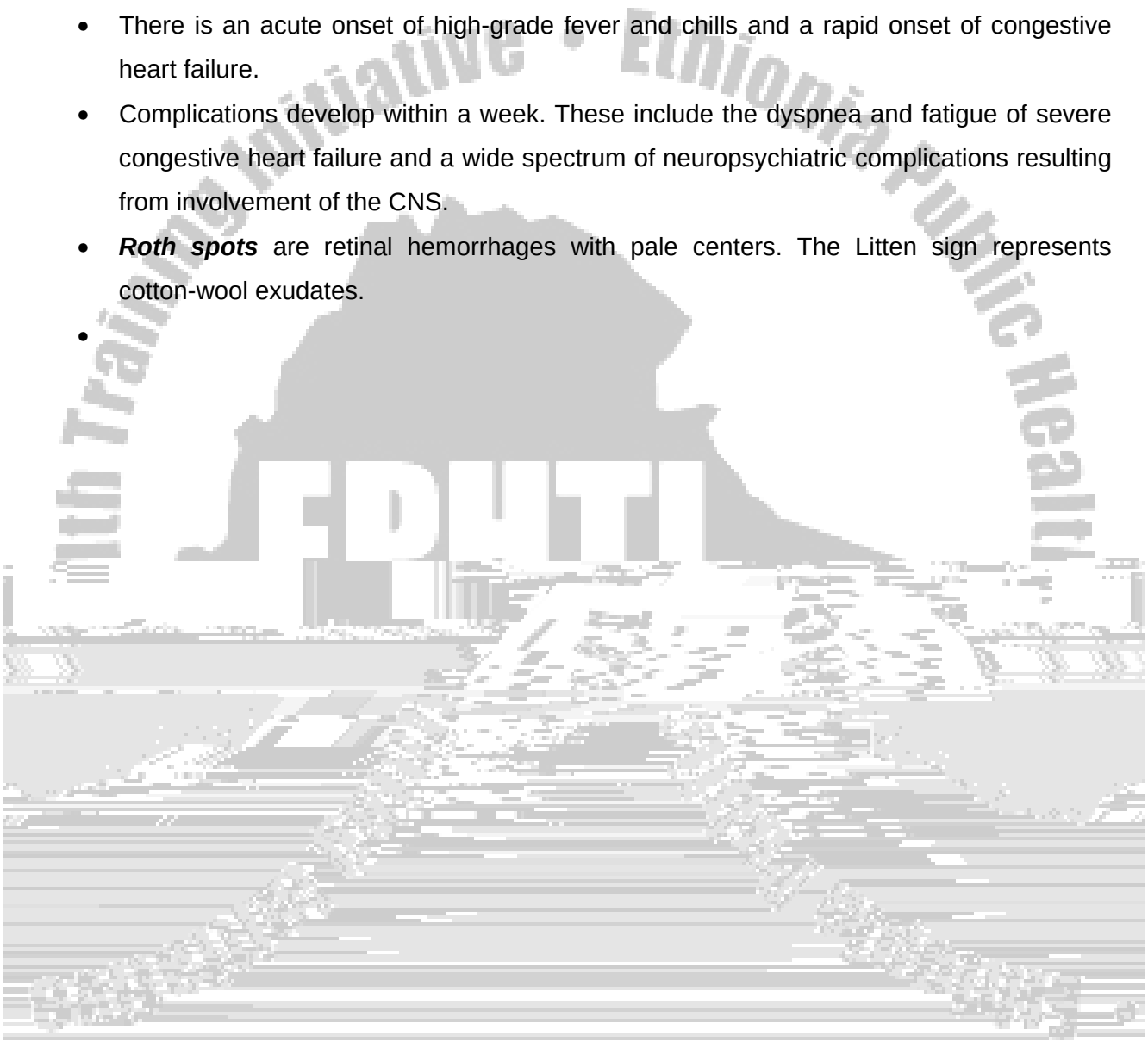

Table III-4-1: Frequencies of Occurrence of prominent Clinical and Laboratory Manifestations in Endocarditis

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:

- 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.

- ***Electrocardiography*** may detect the 10% of patients who develop a conduction delay during infective endocarditis by documenting an increasing P-R interval.

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***:

Minor Criteria
• ***Predisposition***: predisposing heart condition or IV drug abuse • ***Fever*** >38.0 ^{o}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:

- No special diets are recommended for patients with endocarditis; however, if the patient has congestive heart failure, sodium-restriction may be necessary.
- 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
-

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5. Cardiomyopathy

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

-

- 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.
-

5.2 Hypertrophic Cardiomyopathy

Physical examination:

-

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

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.

2. ***Hypersensitivity and toxic reactions to :***
    - Drugs : Doxorubicin (anti- neoplastic agent)
    - Radiation

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.

- 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:***

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.

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.*

- Hypertension is defined as arterial blood pressure that exceeds 140/90Learning obje7rrcs0.0014 Tc8g

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Some factors that may contribute for the development of essential hypertension include:

- ***Genetic predisposition*** e.g. the exact mechanism has not been established
- ***Environmental factors*** a number of environmental factors have been implicated e.g.

- Myxoedema
- Thyrotoxicosis

Neurogenic :

- Psychogenic
- Increased intracranial pressure
- Acute spinal cord section

- 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:
     - o Angina Pectoris
     - o 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, itphysundeg a 4tr

  4)

- 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.

Diagnostic workup

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

- ***Echocardiography***: to detect LVH

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

- 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.

- *Reducing the diastolic BP to < 90 mmHg and systolic BP < 150mmHg.*

1. ***General measures : non pharmacologic therapy***

Sodium restriction: intake not more than 100 mmol/d (2.4 g sodium or 6 g sodium chloride).

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

Pharmacologic therapy.

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

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.

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

Calcium channel blockers: by modulating calcium release in smooth muscles,

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: –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

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*** :
    - o CBC
    - o Urinalysis
    - o Renal function test
    - o ECG

Treatment "treats the patient, not the number"

General measures:

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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.*

Pericarditis is an inflammation of the pericardium surrounding the heart. Percarditis and cardiac tamponade are clinical problems involving the potential space suitintipermponTc-0.0004 Tw[(4.)-5

Table –III-8-1. Classification of Pericarditis

Clinical classification	***Etiologic Classification***
I. ***Acute pericarditis (<6 weeks)***	
a. Fibrinous	
b. Effusive (serous or sanguineous)	
II. ***Subacute pericarditis (6 weeks to 6***	

- ***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

- CBC with differential
- Elevated erythrocyte sedimentation rate (ESR)
- HIV testing
- Antinuclear antibody, rheumatoid factor

- ***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.

- 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.

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.*

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***

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.

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.
-

Resting angina: is particularly worrisome because it implies decreased supply, rather that increased demand, is causing angina. This suggests possible occlusion is imminent.

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

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

- 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.

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Acute 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:

-

- 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

Emergency management :Management of patients should start before they reach the hospital emergency room

1. General measures

-

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.

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 -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.

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

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
-

- Atropine : 1mg IV may temporarily increase the sinus rate
- Cardiac Pacemaker implantation.

Sick sinus syndrome: The sinus node does not fire its signals properly, so that

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:

-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

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

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.

Wide and bizarre QRS appearing in a relatively normal looking ECG

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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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.

  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

occlusion (as with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome).

. 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.

may be ordered to make specific diagnosis

Intravenous pyelogram

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.

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:

Idiopathic

Represent a response to a known antigenic stimulus (e.g., post infectious glomerulonephritis)

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.

- 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

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.*
   Understand the principle of management of nephrotic syndrome.

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
-

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.

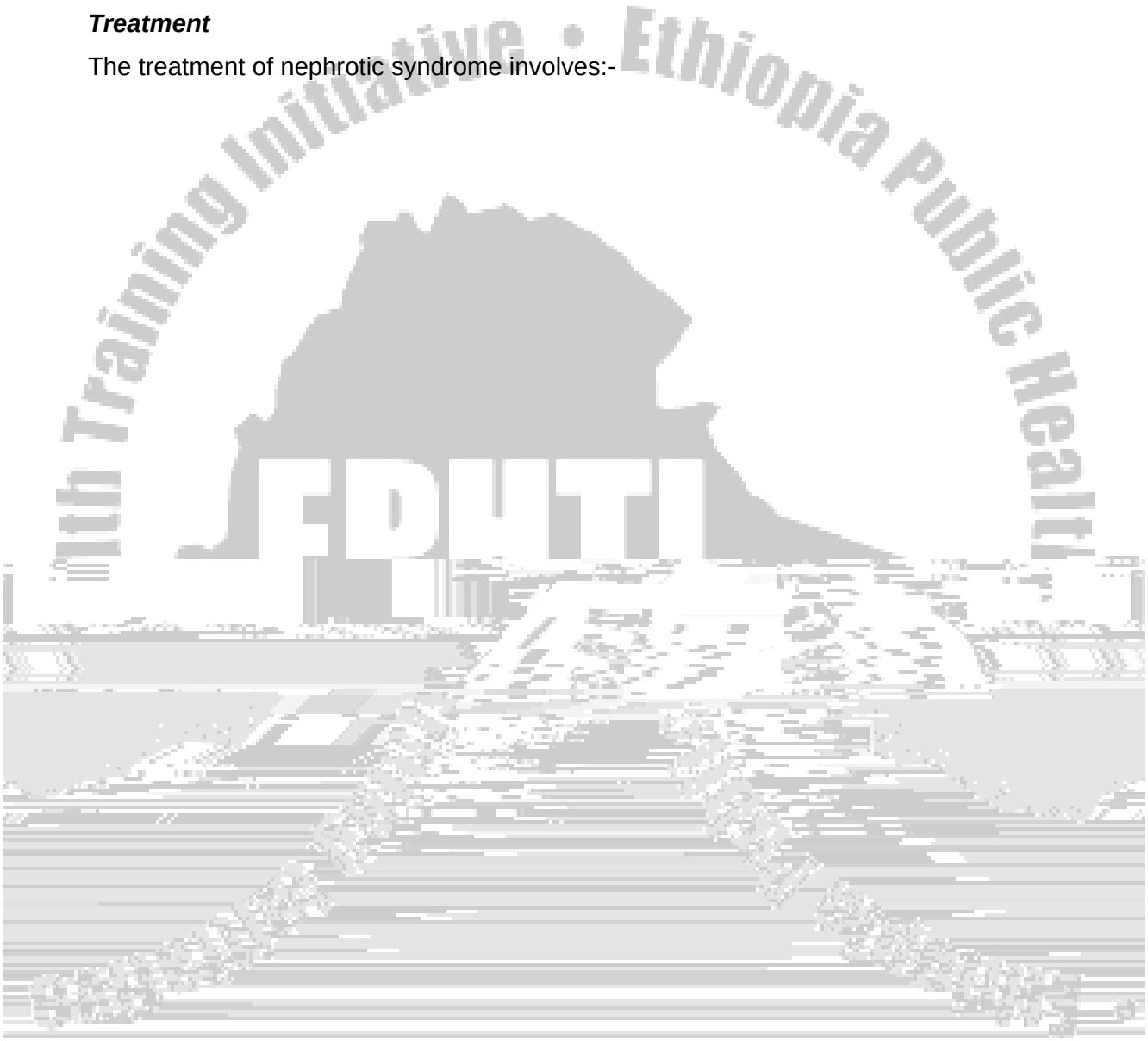
Diagnosis

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:-



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

at the end of this lesson the student will be able to

1. *Define acute renal failure.*

- 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.

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)

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- ***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 :***

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- 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

- ***Metabolic acidosis***: is not treated unless serum bicarbonate concentration falls below 15 mmol/L or arterial pH falls below 7.2.
    - o More severe acidosis is corrected by oral or intravenous sodium bicarbonate. Initial rates of replacement are guided by estimates of

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

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,*

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.
- 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

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:*

- Sometimes sever form of hypertension may occur.

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:

-

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.5.8(ace.)]TJ/TT6 1 Tf-6.9672 -1.7322 TD0 1

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: -

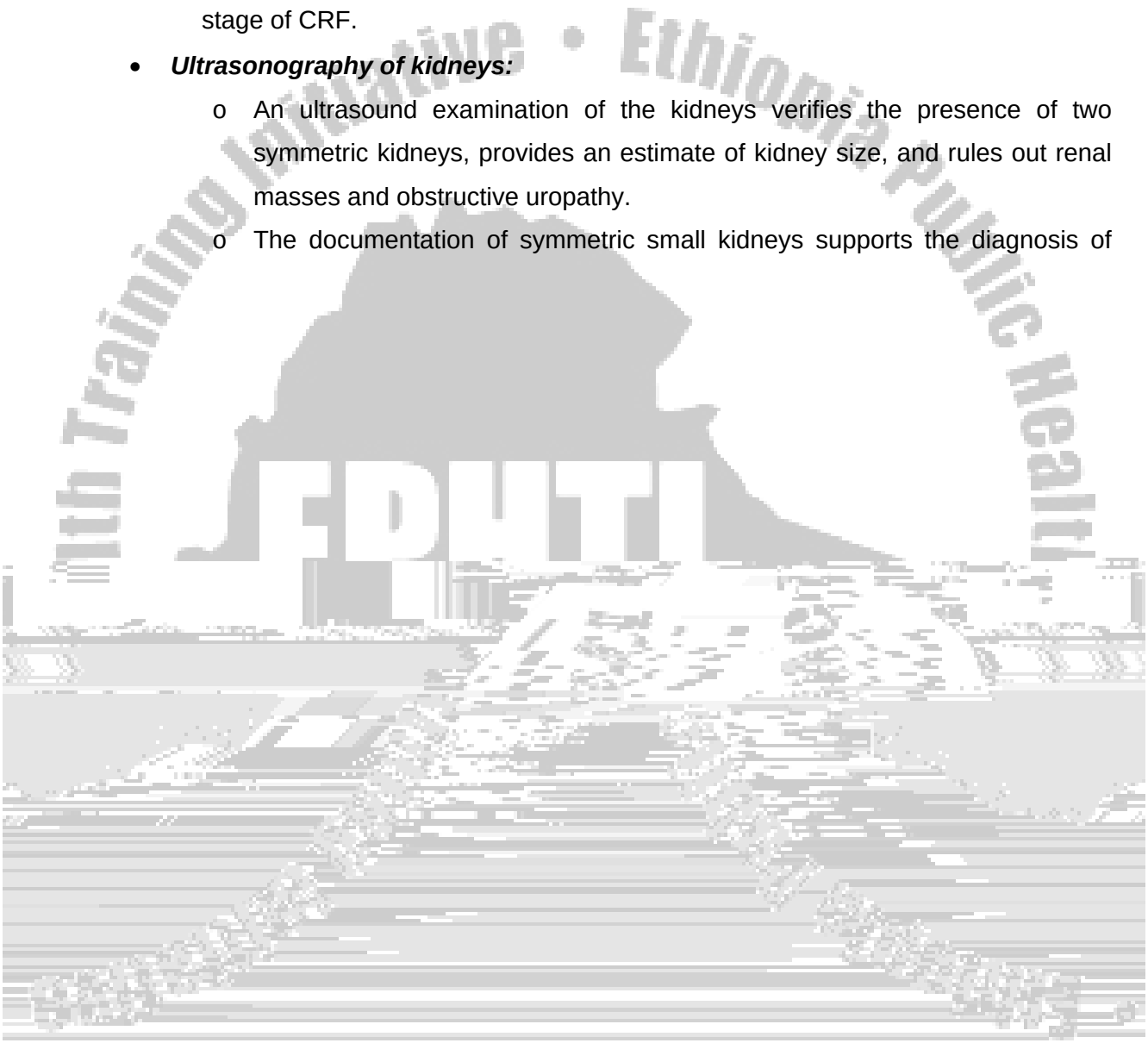
- Particular attention should be paid to:
- Blood pressure
- Funduscopy
- Precordial examination
- Examination of the abdomen for bruits and palpable renal masses
- Extremity examination for edema
- Neurologic examination for the presence of asterixis, muscle weakness, and neuropathy
- In addition, the 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



- *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 :

Volume overload –

- Dietary sodium restriction
- Diuretic therapy, usually with a loop diuretic given daily.

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

about 800 mg/day may be desirable but can be accomplished only by limiting protein intake.

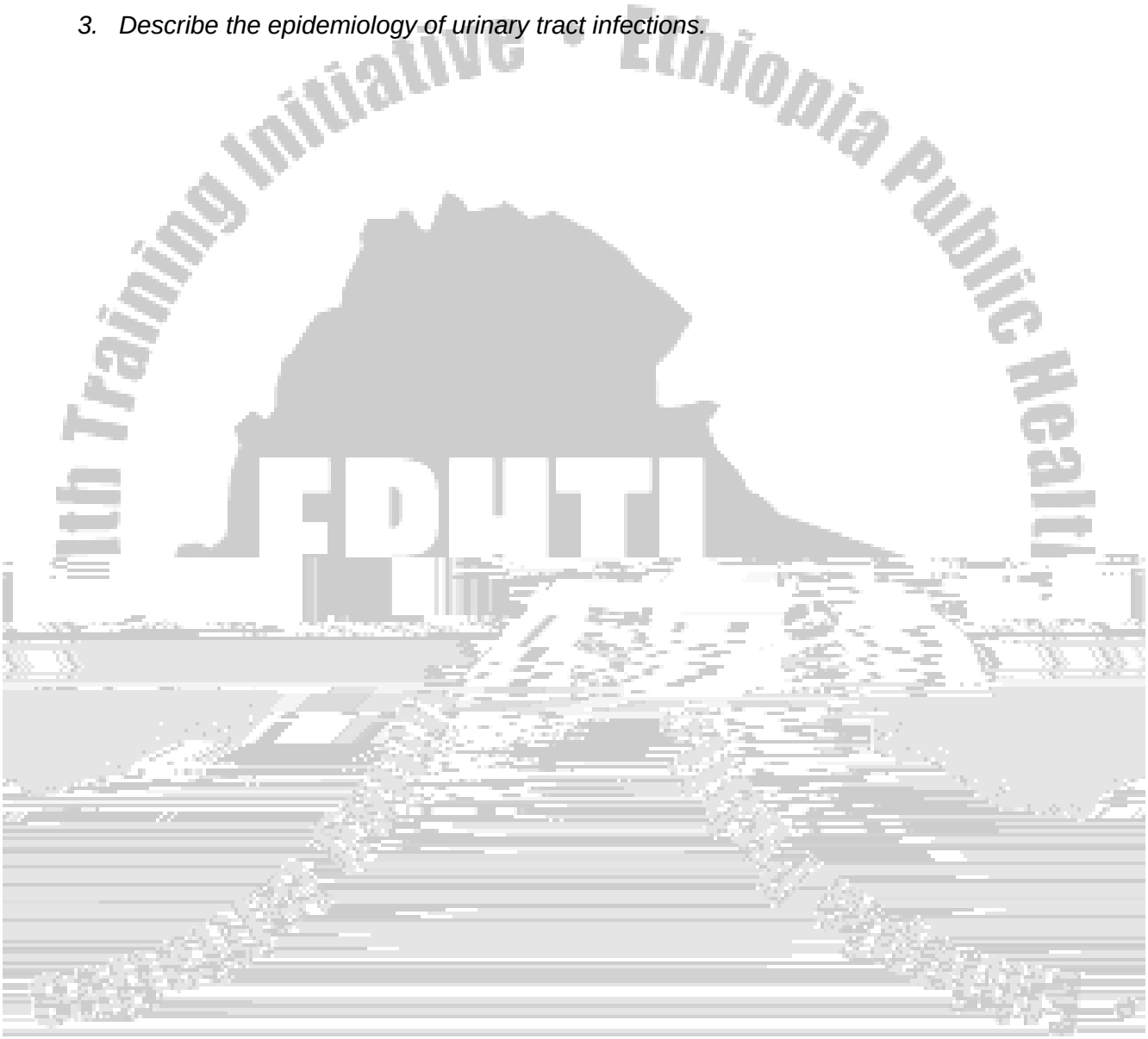
References:

1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition,

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.*



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- *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/ L 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.

Pregnancy

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- 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

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 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

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

Complicated UTI in men and women: *E. coli*, *Proteus*, *Klebsiella*, *PseudeTerr7d.D0.0 d0.0li73l*

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.

Diagnostic work up of patients with gastrointestinal diseases

1) ***Stool microscopy*** ntestinal parasite; ova, cyst or trophozoites, pus cells and red blood cells

   Stool culture - indicated in certain cases of infectious diarrhea

   Chemical analysis of stool est for fecal fat and occult blood

4) Aspiration of peritoneal fluid (abdominal paracentesis) could be:-

- – for evaluation of clinically evident ascites
- – 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:

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- Needle biopsy is done percutaneously

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.

2. Gastritis and peptic ulcer diseases

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, ,
  - 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.
- 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:

-
  - 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.
-
  - 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 *nog9no need to treat*

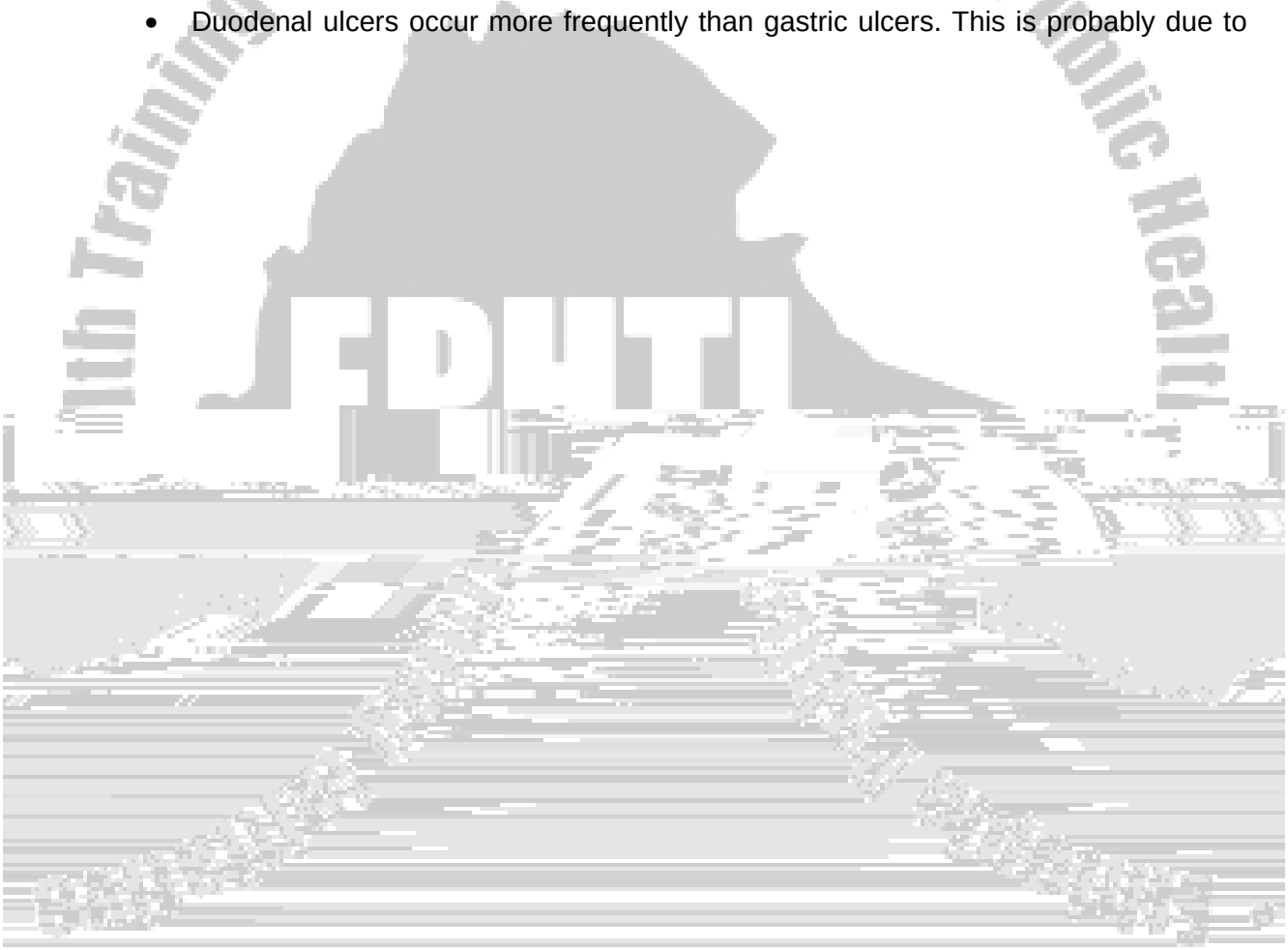
2.2 Peptic ulcer diseases

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



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
    -

- 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.

- ***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
  -

Table V-2-1. Some differences in the clinical manifestations between DU and GU

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.
-
  - May be caus

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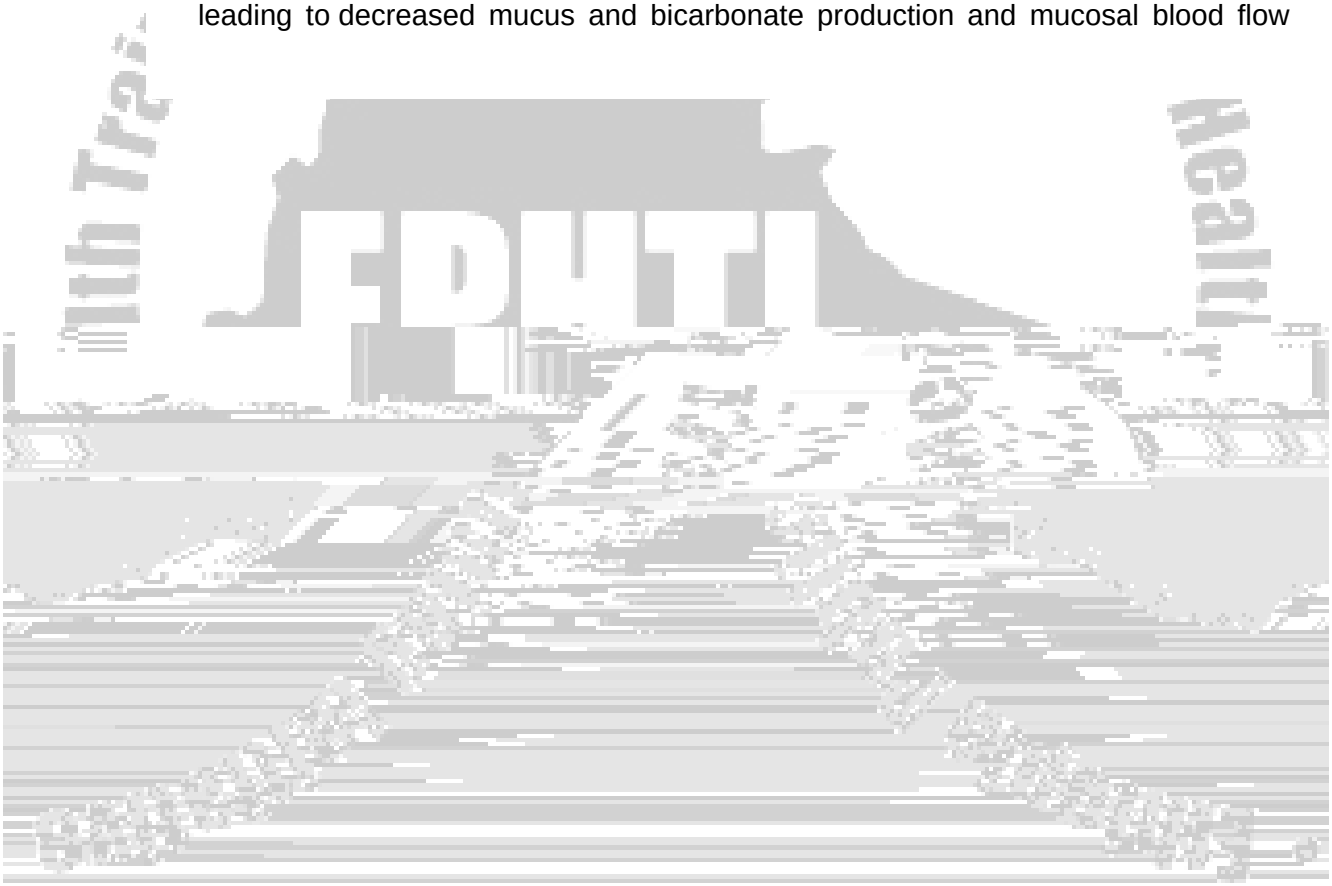
- Gastric cancer
- Gastroparesis
- Gastritis

- In up to 60% of dyspeptic patients no cause is identified (
) - a condition most likely related to an abnormal perception of events in the stomach caused by afferent visceral hypersensitivity.

- 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



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.

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

from extensive small bowel resection. Resection of 50 % of small intestine is well tolerated, if the remaining bowel is normal.

a) Intestinal lymphangiectasia

b) Intestinal lymphoma

a) : 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) : 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.

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

1) 3 - 4 days stool collection is required for this measurement. Faecal fat over 6 g/day is abnormal.
2) 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) 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) 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) is suggested by low serum or RBC folate level with adequate diet and little alcohol intake.
6)

7) 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) 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.

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

- 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:

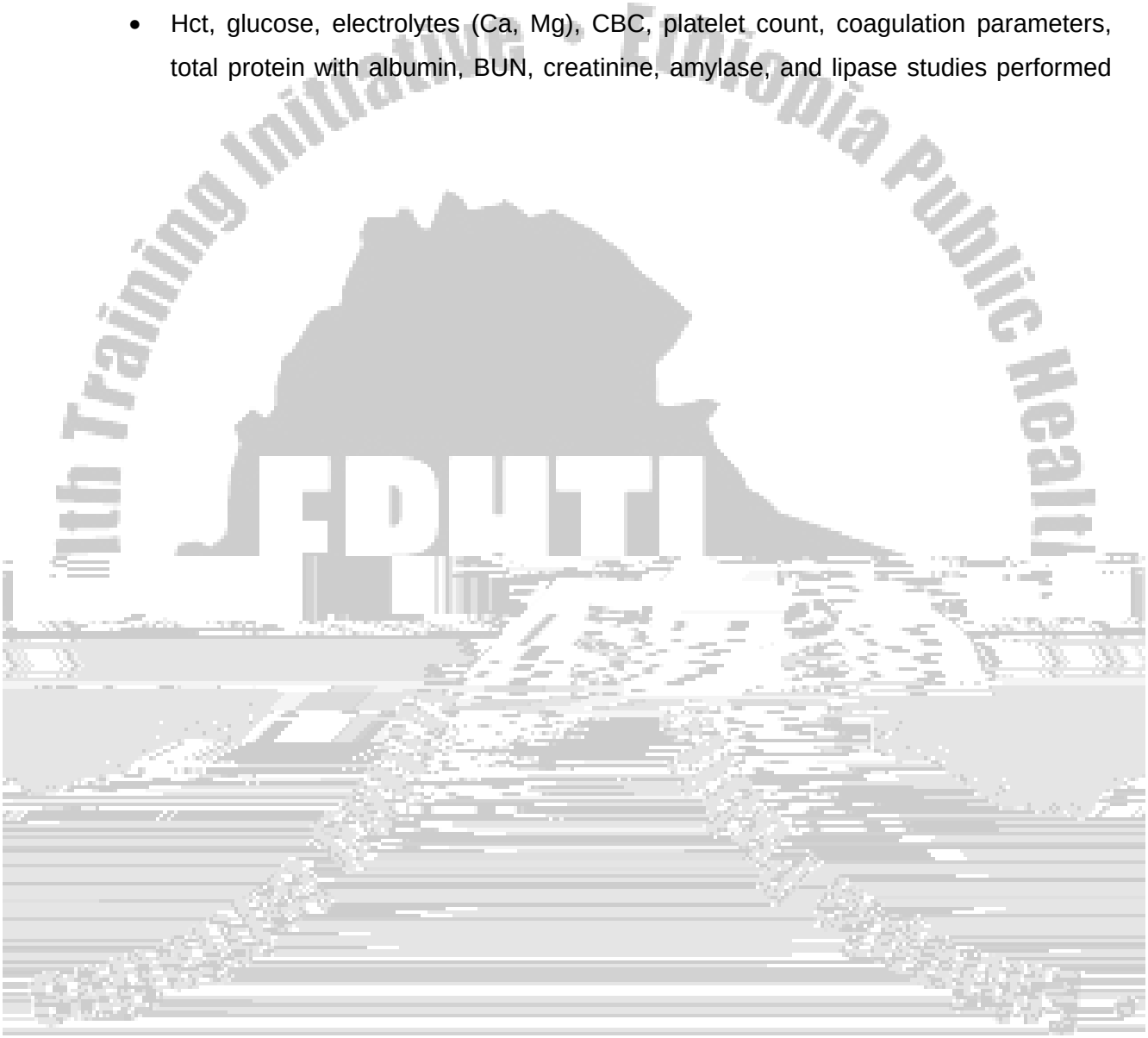
-
- : usually between 12,000 to 20,000/mm^3
- may be as high as 50-55 % due to third-space losses.
-
- is decreased
- may be increased
-
-

Differential diagnosis: the following diseases can mimic acute pancreatitis

- ♦ Perforated gastric or duodenal ulcer
- ♦ Mesenteric infarction
- ♦ Strangulating intestinal obstruction

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

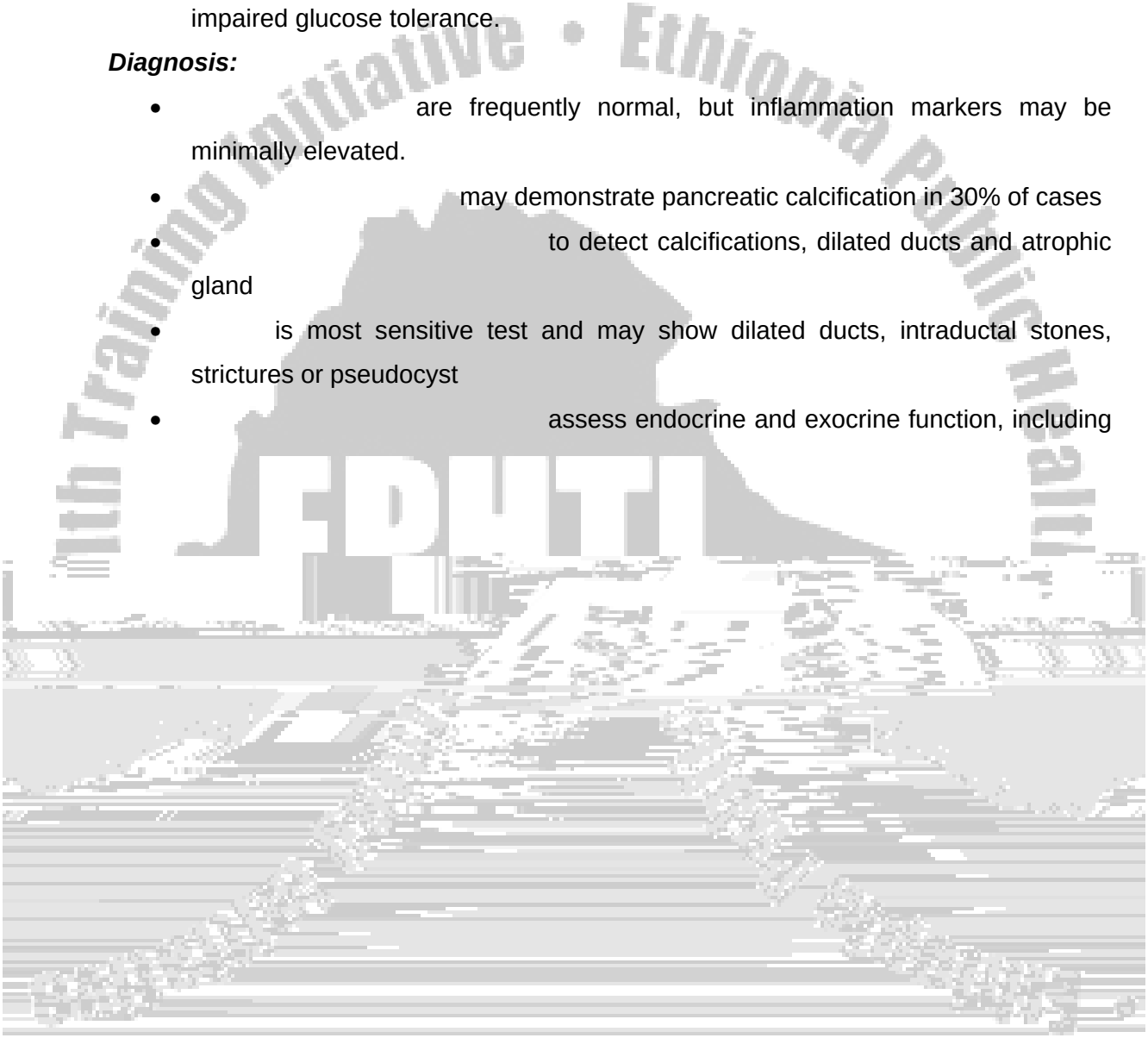


Signs and symptoms

- 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:

- are frequently normal, but inflammation markers may be minimally elevated.
- may demonstrate pancreatic calcification in 30% of cases
- to detect calcifications, dilated ducts and atrophic gland
- is most sensitive test and may show dilated ducts, intraductal stones, strictures or pseudocyst
- assess endocrine and exocrine function, including



5. Hepatitis

Learning objectives: at the end of this unit the student will be able to

1. *Define acute and chronic hepatitis*

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).
-

- Arthritis and urticaria may be present particularly in HBV which are attributed to immune complex deposition.
- , 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***

(2) indicates HBV replication and high chance of infectivity to others

ii) ntibodies

(1) – confers long term immunity

(2)

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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. : 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. : 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.
-

- 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.

- 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.

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. - inflammatory activity is confined to portal areas.
2.

Ç€ Hepatitis C can be treated with interferon Ä@ and ribavirin

er and its complications Ç€

Internal Medicine

- 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 -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.

- Occurs in the setting of fulminant hepatitis
- Cerebral edema plays a more important role
- Mortality rate is very high

- Occurs in chronic liver disease
- Often reversible

- 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	

- CNS depressant drugs

2) Reduce and eliminate substrates for the generation of nitrogenous compounds.

- *Restrict dietary protein*
  - o For patients in coma no protein should be given
  - o 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.

- 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.

Clinical and Laboratory findings

Common symptoms and findings

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***

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:

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d) *Shigella dysenterae* may initially cause secretary 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.

- 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.

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 Norwalk and Rota viruses

- Invade and damage villous epithelial cells

inflammatory Bowel Diseases (ulcerative colitis), irritable Bowel syndrome, colonic cancer, and immuno suppressions like AIDS.

is there any relation to any part of the day?

Nocturnal – organic causes

Non nocturnal – functional causes like irritable bowel syndrome

Bloody diarrhea is usually inflammatory or ischemic in origin and caused by invasive organisms, ulcerative colitis, or neoplasms

Large volume diarrhea indicates small bowel or proximal colonic diseases

Scanty, frequent stools associated with urgency suggest left colon or rectal diseases

? 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

Penicillin may be associated with psudomembraneous colitis.

Laxatives

Chemotherapeutic agents

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

- 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

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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*

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

  ⇒ This allows more O_2 to be unloaded from the RBC at any given blood O_2 tension

2. Cardiovascular adjustment

- occurs at Hgb level of 7-8 gm% : the increased in cardiac output coupled with modest creates a hyperdynamic state and hence systolic ejection murmur
- 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 ⇒ ↑ O_2 extraction at peripheral tissues

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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)

- 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

- 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

- Stomach acidity, Ascorbic acid, citrates, while
- 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*

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

⇒ 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)

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

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. and

months

Etiologies

1) Chronic inflammatory diseases

a)

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

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

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.

2. Leukemias

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*

- 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.

- 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

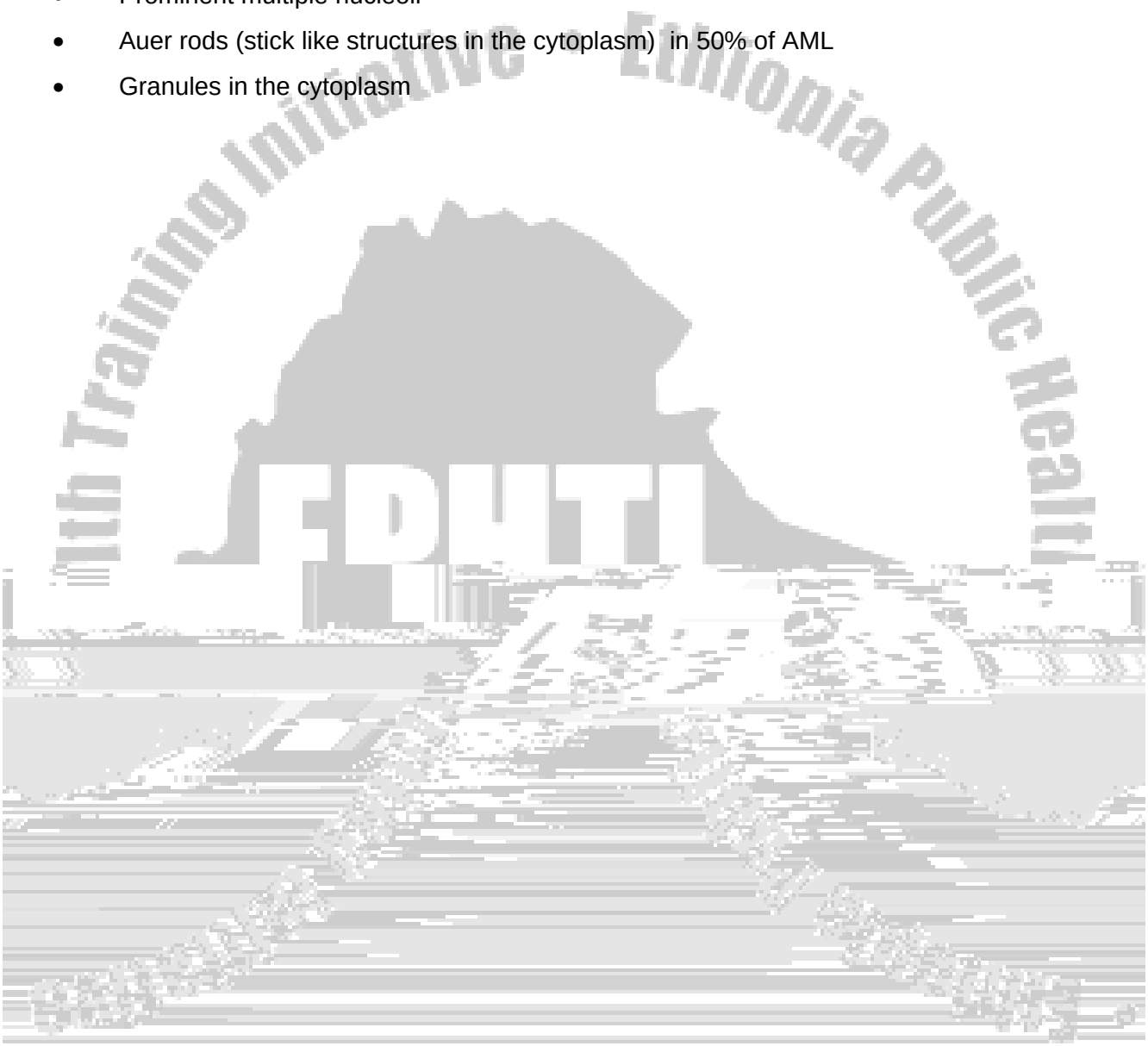
Differentiation between ALL and AML is critical because the two have different

- Natural history
-

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



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  - 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.

The definitive diagnosis of acute leukemia is made on the basis of peripheral blood film and bone marrow aspirate examination. The following td niondetecteLaboratoryss thof

Table VI-2-1 Showing the main features of acute leukemic cells

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.

of acute leukemia's is divided in to four phases

Remission induction is characterized by intensive systemic chemotherapy with the goal of reducing leukemic cell below the level of clinical des 629.1 Tm0c9ET89. bo

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.

: FAB suggested 3 types of CLL

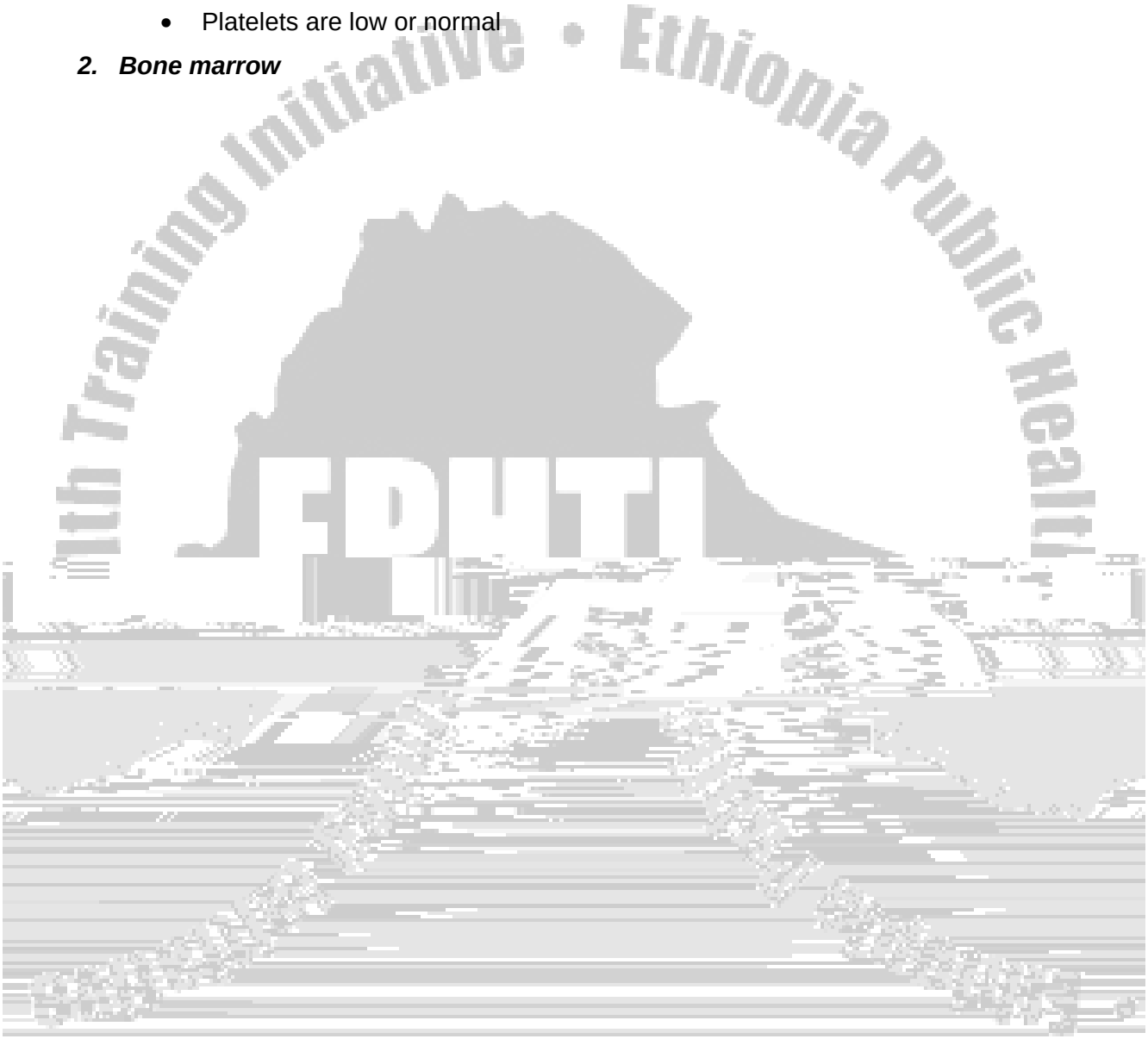
1. ***Typical CLL:*** - where more than 95% of lymphocytes in the blood are small lymphocytes.
2. ***Prolymphocytic CLL:-*** If ≥ 51% of lymphocytes in the blood are prolymphocytes
3. ***Atypical CLL*** :- if < 10% of lymphocytes in the blood are small lymphocytes

Clinical Features

In 25% the diagnosis is made incidentally in asymptomatic individuals when WBC count is done

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***



NB: The cervical, axillary and inguinal lymph node groups (unilateral or bilateral), the spleen and the liver each counted as one area.

- Stage 0 and 1 CLL has good prognosis. If a patient has stage 0 disease without

Response to treatment can be assessed by

- Declining WBC count
- Increase Hgb, platelet count
- Decrease size of Lymph nodes

D) Chronic Myelocytic Leukemia (CML)

: 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.

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

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.

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:-

- <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.

- 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

- 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

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3. Lymphomas

: 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

- 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

- 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 cha5l2 TD.7(d it descr)6.6(ib)5.7(ed as Pel –)5.7(ebsteins f)6.1(e)5.7(ver)]TJT*009 Tc0 Tw(Clini

- Others symptoms include Weight loss, profuse sweating, weakness, fatigue, anorexia, cachexia

- Normocytic normochromic anemia
- 1/3rd of patients may have leukocytosis
- Eosinophila
- Lymphopenia may be found in advanced disease
-

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. – mainstay for stage I and II diseases; used for stage III and IV

.

2.

- Cyclical chemotherapy for stage III and IV diseases
- In stage I and II patient with bulky disease

E.g. - Mediastinal widening by 1/3rd

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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*

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.
-

- 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

-

Less commonly

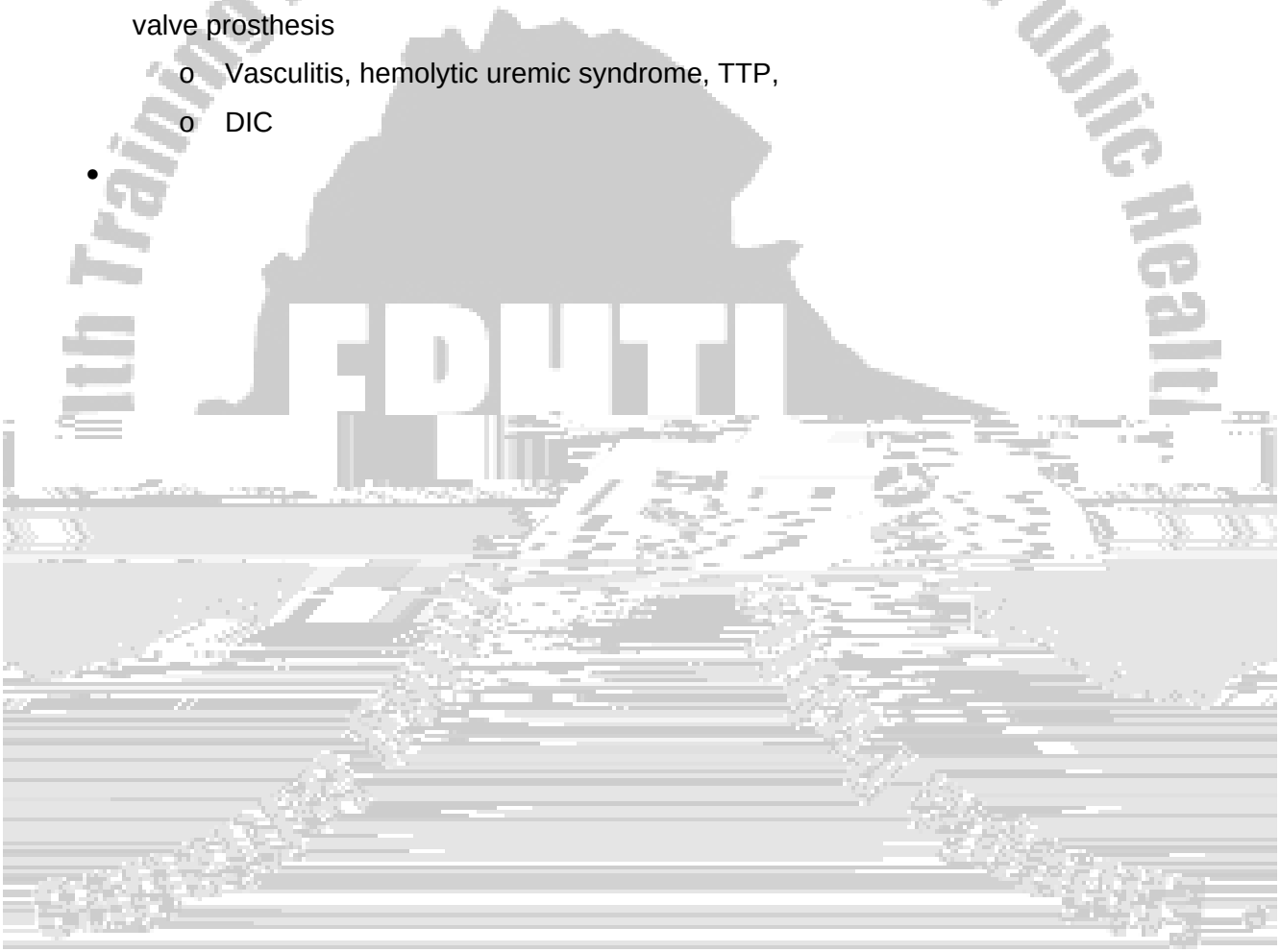
- Cytotoxic drug use
- Rarely congenital megakaryocytic hypoplasia and thrombocytopenia

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:

- :- associated with abnormal vessels, fibrin thrombi and heart valve prosthesis
  - Vasculitis, hemolytic uremic syndrome, TTP,
  - DIC
-



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.

- 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

- 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.

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:***

- : benign disorder seen in women of child bearing age.
- : due to atrophy of connective tissues of cutanous vessels
- : follow vascular damage by infecting organs or immune complex deposit e.g. meningococcemia, dengue fever.
- : 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
-

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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

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

- Desmopressin

References:

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

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.

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 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

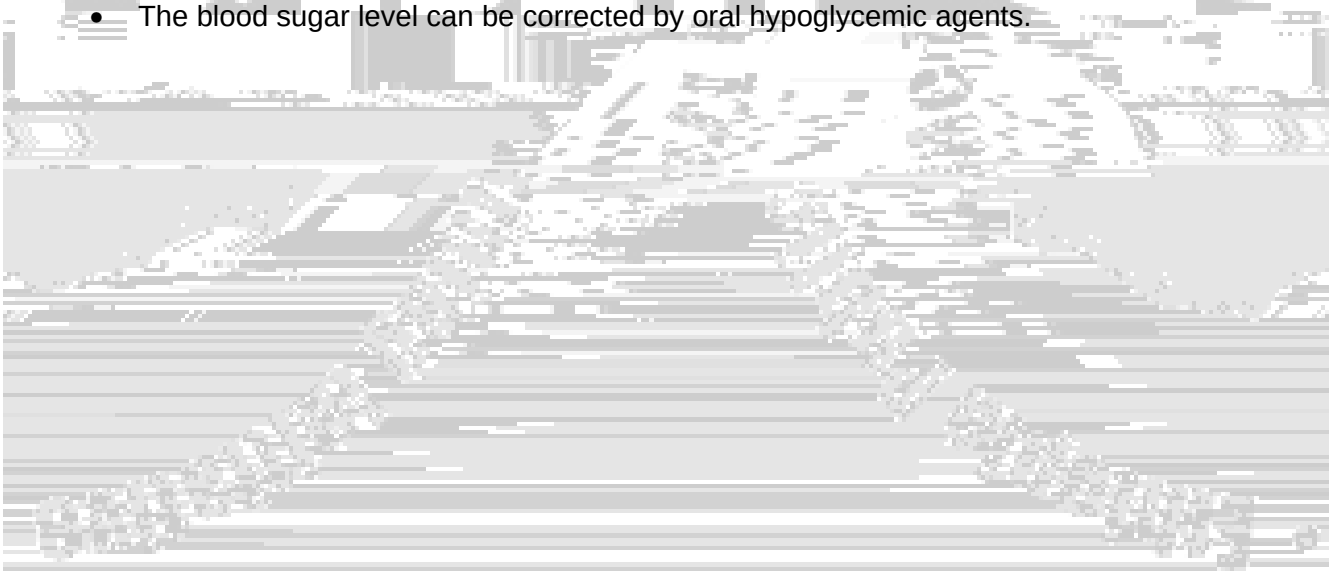
- Pancreas: produces insulin and glucagon
- Liver: produces somatostatin
- Kidneys: produce : renin, angiotensin, erythropoietin, Vit-D
- Stomach: produce gastrin

execute the command delivered by hormones.

- 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 -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

(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.



- 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 -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 -cell antigen. or instance Coxsackie virus antigen and that of glutamic acid

decarboxylase (GAD) found within the -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 .

- 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 " " period.
- This is unfortunately is transient and the patients will be needing insulin again when the progressive destruction of -cells leads to absolute insulin deficiency.

Mechanism of Type 2 disease:

- impaired GTT followed b9seline D0 pheTD0oe g5.4

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

: ***Insulin resistance:*** *increased glucose and Non Esterified Fatty Acids (NEFA*

: ***Increased insulin secretion*** *compensatory hyperinsulinemia*

Impaired glucose tolerance

: ***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.

- Polyphagia: feeling of hunger , a need to eat several times a day
- Generalized weakness-
- Weight loss

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:

- ***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

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  - 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.
-

- 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.

- 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

-

- The effectiveness of sulfonylureas declines up to 10% annually as the failure of beta-cell function progresses.

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.
    - : 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.

- ***Acarbose and Miglitol***: are oral agents that reduce the absorption of

,

- 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.

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

Hypoglycemia in the diabetic patient is caused by

- Overdose of insulin or hypoglycemic agents
- Missing of meal
- Strenuous exercise

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, -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. *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.

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***

  BUN, creatinine,

  CXR, urine culture and sensitivity, blood cultures should also be done to identify an infectious process.

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 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. :

- 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.

- as well as urine output hourly.
- should consist of 0.45% (½ strength) saline with additives as indicated; 150 to 200 ml/hr adjusted according to urine output.
- including infection, pregnancy, Myocardial infarction, inappropriate use of insulin.
- 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.

Hyperglycemic Hyperosmolar State (Non-Ketotic Hyperosmolar Coma)

- Usually occurs in elderly type 2 DM patients that do not develop ketosis.

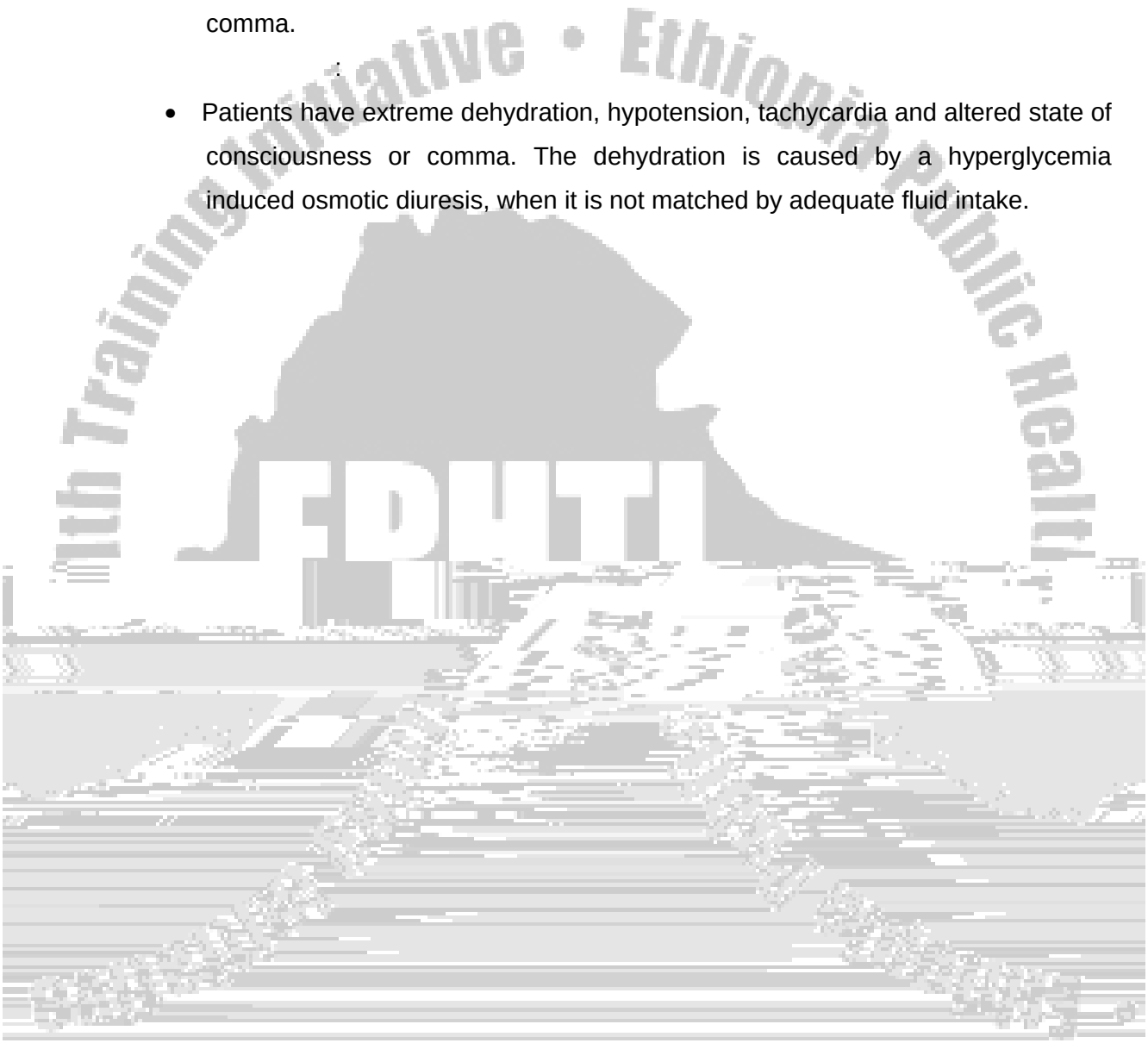
- It is often precipitated by serious intercurrent illnesses such as myocardial infarction, stroke, pneumonia, sepsis etc.

  :

  - 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.

    :

  - 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.



- -increased permeability of capillaries and from ruptured aneurysms
- proteins and lipids leak due to increased permeability of capillaries

Maculopathy: which manifests with impairment of central vision loss

asymptomatic unless complicated by hemorrhage

- Characterized by new vessels formation which is stimulated by ischemia

: 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

include

- Burning sensation, numbness
- Constipation or nocturnal diarrhea
- Impotence
- Foot ulcer

Classification of Diabetic Neuropathy

- 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.

: characterized by neurogenic pain. It is often self limiting

: atrophy of proximal muscles mainly around the hip girdle

may manifest with

- Postural hypotension
- GI manifestations: gustatory sweating, gastroparesis, nocturnal diarrhea
- Genitourinary manifestations: neuropathic bladder, erectile dysfunction (impotence)

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

- 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

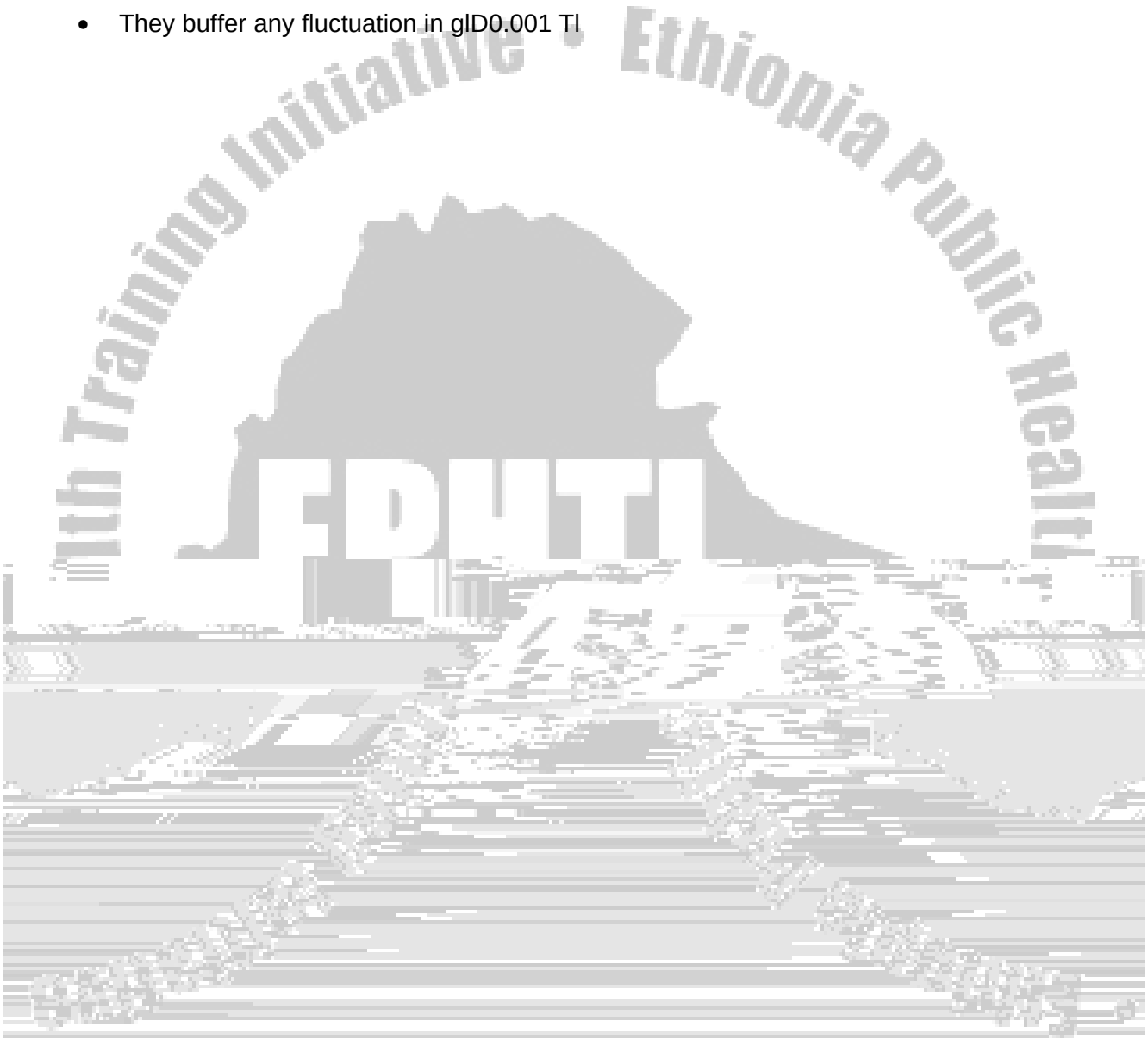
- ***Neuropathy***
  - Loss of pain sensation exposes to injury
  - Loss of sweating results dry skin that is susceptible to injury
- ***Vascular:*** poor blood supply to the foot causes decreased healing of wound poor recovery from secondary infections.
- ***Abnormal Pressure loading***: due to neuropathy (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

- 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 glD0.001 Tl



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.

The patient may complain tearing, eye irritation, pain and double vision. In sever case vision may be threatened.

- ***Other findings***

- 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.

- Skin rash or joint pain
- Agranulocytosis

- Hospitalization , surgery and anesthesia are avoided
- The occurrence of post treatment hypothyroidism is less likely

- Permanent remission occurs in fewer than 50 % of patients
- Treatment success depends on patient compliance to treatment

- , 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.

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.

- usually reserved for those who are unable to take antithyroid drugs

- 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:

- 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.

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- Pericardial effusion and ascites occasionally occur

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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

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.
-

- 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.
-

- If thyroid enlargement persists despite adequate TSH suppression, a needle

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;

-

- 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

- ***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,
  - 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.

- 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

4. Diseases of the adrenal gland

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

-

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

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

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- 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

: is a syndrome associated with hypersecretion of the mineralocorticoid, aldosterone.

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***

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.

- ***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

4. Diseases of the pituitary gland

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

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

Infiltrative diseases: Sarcoidosis , hemochromatois ,

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,

- 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) 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
  - o

1) Treatment of the underlying cause the patients pituitary insufficiency

- 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) : treatment is directed toward replacing the hormones of the hypofunctioning target glands.

- : given for children with growth failure
- : given in usual replacement dose
- is given in the usual replacement dose
- : may be given to women to restore menstrual function and Testosterone may be given toen to re 6(After surgical9 cvS009 p(rans

pAtiehnticeaglucarlydition in which one or m009 pituitary hormones are deficient; may represent an

- 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.
- 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.
- 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

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:

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.

- ***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

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IV) Posterior Pituitary lobe Disorders

Central Diabetes Insipidus

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 area:*** may result from head trauma, neurosurgical procedures such as hypophysectomy.
3. ***Less common causes***

started in the morning by weighing the patient, obtaining venous blood to determine electrolyte concentrations and osmolality, and measuring urinary

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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

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:***

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

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.

- 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

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.

is a serotonin agonist that decreases substance P release at the trigeminovascular junction.

- Widely used for relief of acute attacks
- Has oral, sublingual, rectal, nasal and parentral preparation. Parentral forms are used for rapid relief of the attack.
- Usually prepared combined with caffeine which potentiates the effect by improving absorption.
- ***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
- ***Side effects:*** are nausea, vomiting, myalgias, chest discomfort, peripheral ischemia and even angina. Excess use may lead to rebound headache and dependency
- ***Contraindication:*** patients with vascular diseases like coronary heart disease

(Naratriptan, Ritatriptan, Sumatriptan, and Zolmitriptan): are new drugs in management of migraine.

- ***Sumatriptan –*** single 6 mg SC dose is effective in 70 – 80% of patients

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 -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.

- 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

- Inhalation of 100% oxygen and
- ***Sumatriptan*** 6 mg S.C. stat said to be helpful and ergotamine or other analgesics may also be used.

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***

-
    - 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.

-
  - 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.

Physical Therapy: different techniques can be used including

- Hot or cold application
- Positioning
- Stretching exercises
- Traction
- Massage

- 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:***

2. Diseases of the Spinal cord

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.

- ***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.

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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

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.
- 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

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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.

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:

- It affects predominantly young men.

3. Cerebrovascular diseases

at the end of this lesson the student will be able to

1. *Define cerebrovascular diseases/stroke.*

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*

Goals /Steps

Assessment and maintenance of vital functions
Determination of presumptive diagnosis of stroke subtype
Confirmation of stroke subtype
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:

- ***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 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.

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.
-

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

- 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

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

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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- 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.
- 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	
Spontaneous	4
To verbal stimulus	3
To painful stimulus	2
None	1
Best verbal response	
Oriented	
Confused	

Inappropriate words Unintelligible words None	
Best motor response	
Obeys commands Localizes pain Withdrawal from pain Extensor response Flexor response None	

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)

- 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:

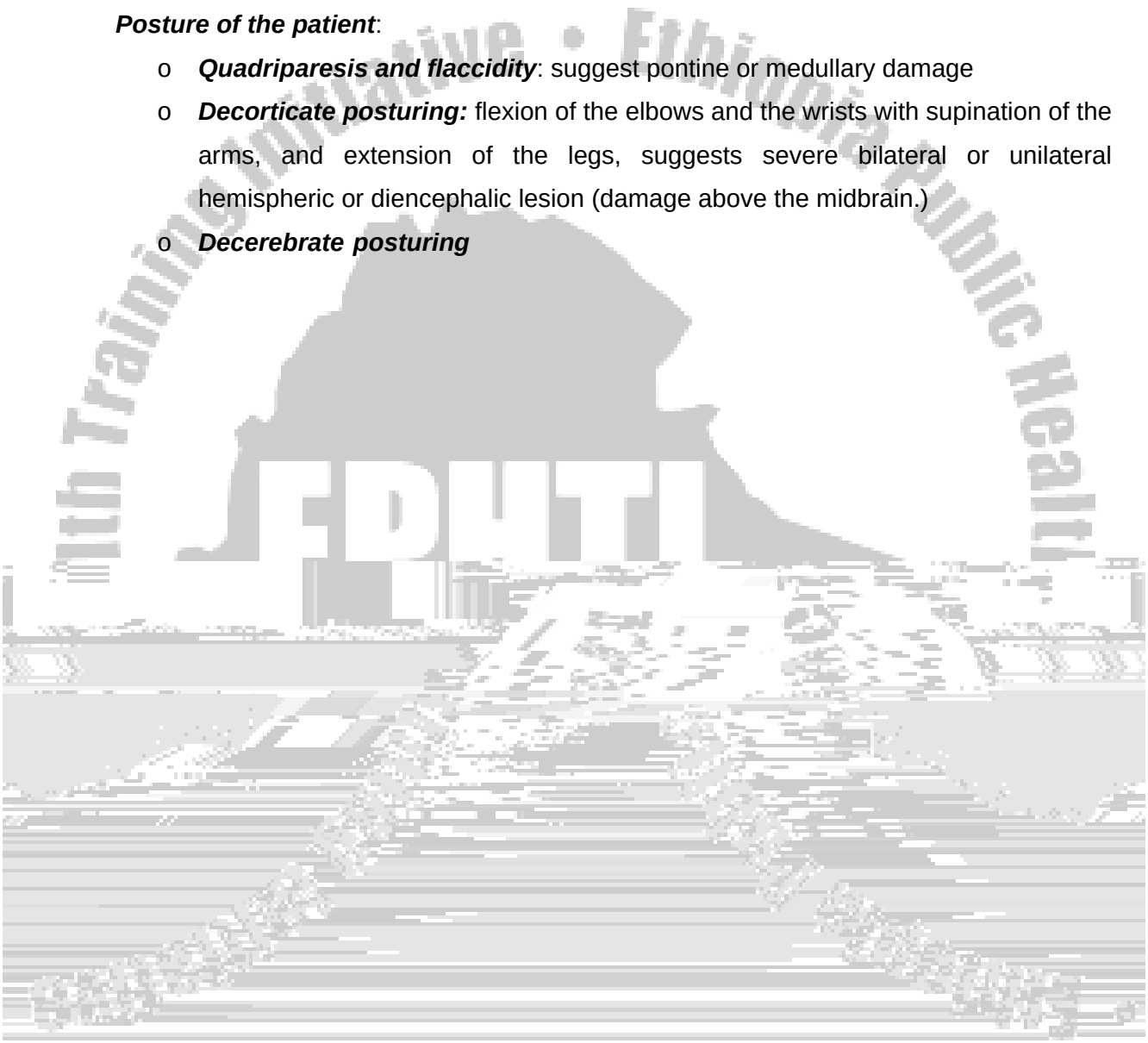
- Abnormalities of respiratory pattern can help in coma diagnosis but are of less localizing value in comparison to other brainstem signs.
  - ***Shallow, slow, but regular breathing*** suggests metabolic or drug depression.
  - ***Cheyne-Stokes respiration*** signifies bihemispherical damage or metabolic 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***



- ***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)

- If there is possibility of cervical fracture, immobilization of the neck is essential
-

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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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.

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)

- 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 respir

- ***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
-

- 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.

- ***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:

- 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

- ***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

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.

- 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

- 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

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

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.

6. Parkinson's Diseases and other movement disorders

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.

- 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

- 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)

- *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.

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
- may manifest with orthostatic hypotension, constipation urinary urgency and frequency , excessive sweating
- ***Depression*** affects approximately half of patents
- ***Anxiety***
- ***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***

- 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.
-

The dosage of these drags should be escalated gradually

Wearing- off effects: management of Parkinson's disease becomes increasingly difficult

- 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

- 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.

- Correct underlying metabolic abnormalities.
- Clonazepam 0.5-2 mg PO. TID or valproate may be effective.

Tics

- Brief, rapid, simple or complex involuntary movements, which are stereotypical and

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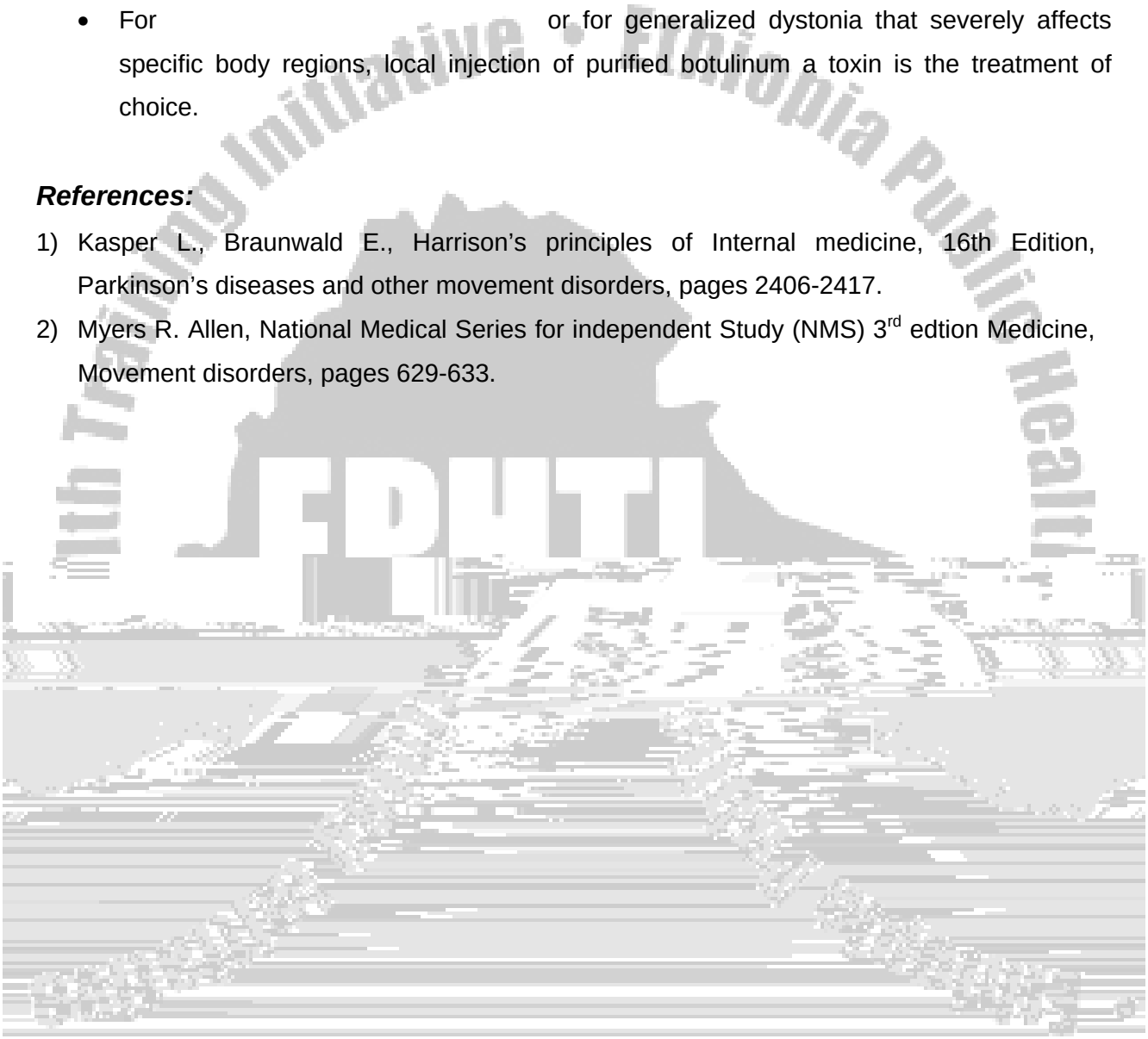
Treatment is often unsatisfactory.

- For 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 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.



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

Diabetes mellitus Leprosy

Uremia

Alcohol abuse

Vitamin deficiency: Vit B1, B6, B12

HIV

Hereditary neuropathies 245 TD-0.0012enj6(Su330.3fig5 Tw[s1 1Cg5

		Diabetes mellitus Uremia Vasculitis Hypothyroidism Paraprotinemias CIDP Drugs Toxins
	Guillain-Barre syndrome Porphyria	Diabetes mellitus Amyloidosis Familial dysautonomia

- ***Trauma***: most common cause of localized injury to single nerve
-

- 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

-
- e.g. megaloblasts in pernicious anaemia may suggest Vit-B12 deficiency or stippled RBCs indicate lead poisoning.
-
- creatinine to assess for renal function test
-
-
- (e.g. multiple myeloma)
- if suspicion of thyroid dysfunction
-
- 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

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

Immunotherapy:

- ***Plasmapheresis:*** can shorten the length of time that the patient is dependent on

8. CNS infections

- ***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;

- 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.
-

Note: These classic meningeal signs may not be seen in infants, old persons and patients in coma.

- 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.

- 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

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.

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.

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:

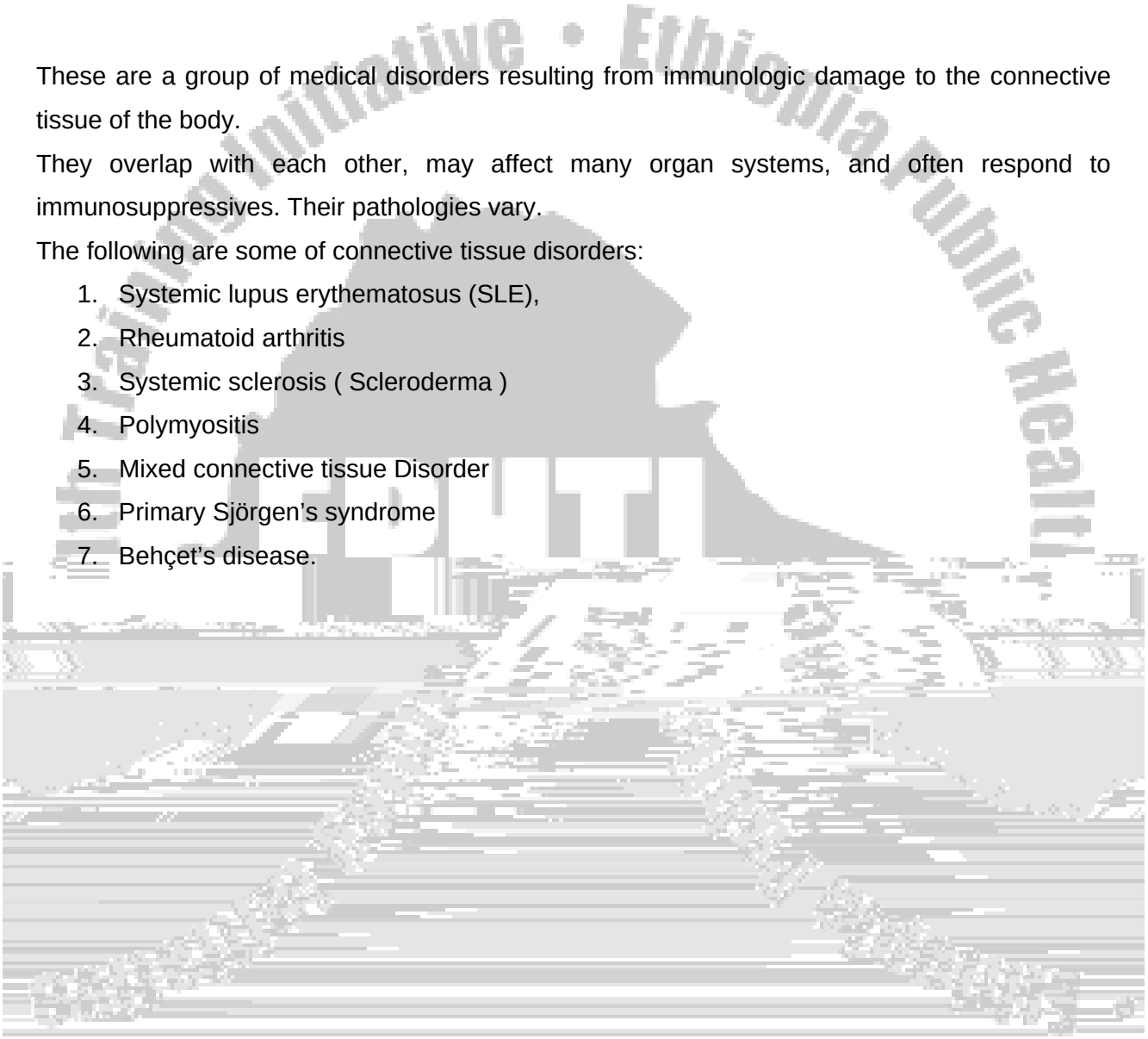
1) Kasper L., Braunwald E., Harrison's principles of Internal medicine, 16th Edition, Meningitis and Encephalitis , pages 2471-2489.
2) Myers R. Allen, National Medical Series for independent Study (NMS) 3rd edition Medicine, CNS infections, pages 644-645.

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) 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 :

a) Fatigue , weight loss and fever are prominent systemic complaints

b)

- 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)

- Joint/muscle pain, non-erosive polyarthritis
- Myositis, proximal myopathy,
- Aseptic bone necrosis

d) SLE cause diffrent types glomerulonephritis which may manifest with proteinuria, casts, edema, and later on to Cronic renal failure (uremia)

e) 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)

- Pleurisy,
- Lupus pneumonitis,
- Fibrosing alveolitis

g)

- Hypertension from renal involvment

- Pericarditis,
- Non infective endocarditis
- Myocarditis
- Coronaty vessle Vasculitis

h) anemia, leukopenia, lymphopenia, thrombocytopenia, increased ESR

i) intestinal vasculitis , Pancreatitis

j) fever, splenomegaly, lymphadenopathy, recurrent abortion

1) 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)

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

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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

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:

Short term : Controlling pain and reducing inflammation without causing undesired side effects

Long term: Preservation of joint function and the ability to maintain life-style.

A)Pharmacotherapy

1) First line Treatment: 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.

- 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

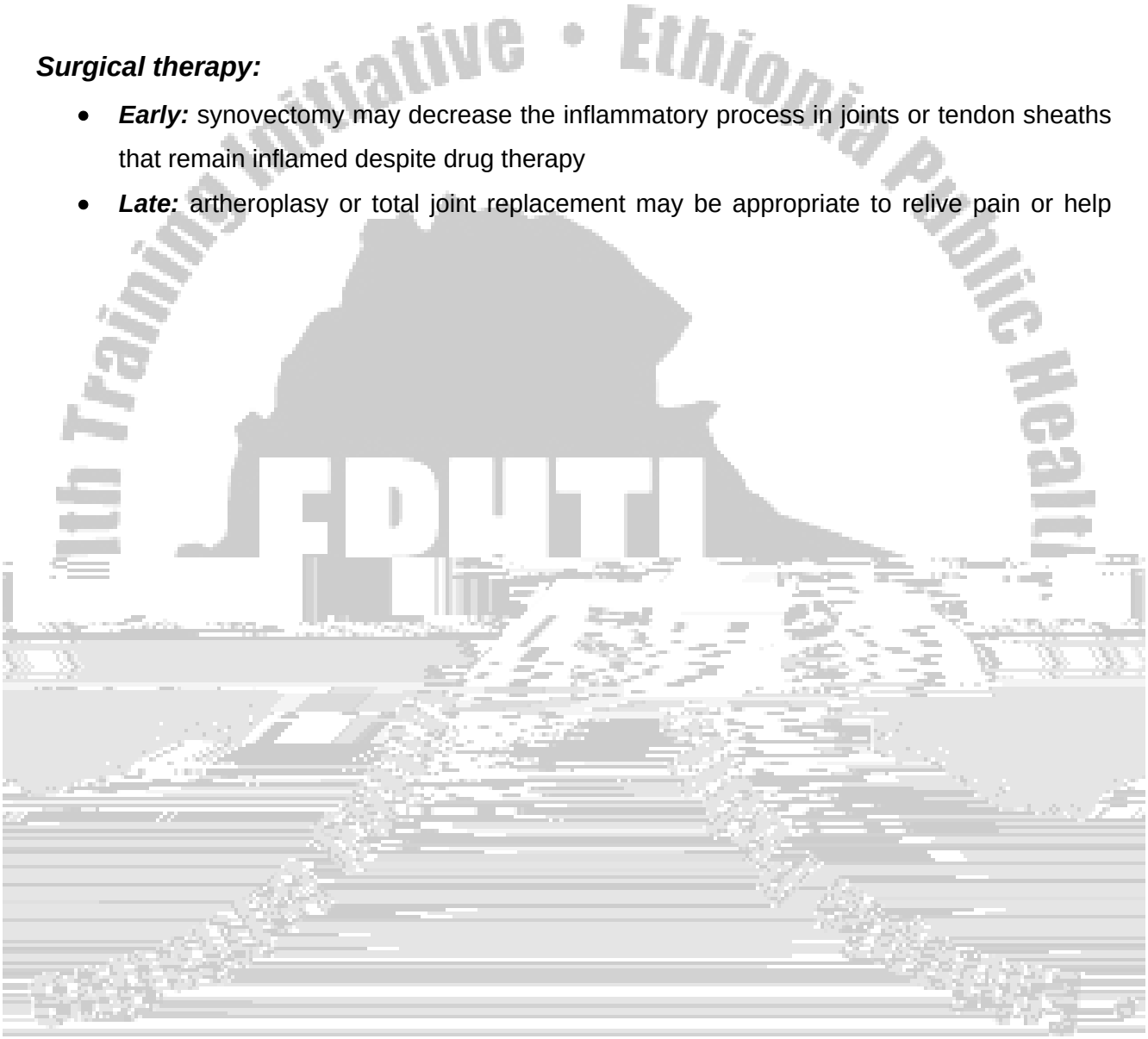
2) ***Physiotherapy and occupational therapy*** to reduce disability

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



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

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.

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- ***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.

- Muscle enzyme (CK)is elevated

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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***

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

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

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