Medicine summary file

This file was done by:

- Razan Alrabah
- Taif Alotaibi
- Lama Alzamil
- Sedra Elsirawani
- Amirah Alzahrani
- Ghalia Alnufaei
- Njoud Alali
- Shahad Selayem
- Ajeed Alrashoud
- Rahaf Alshabri
- Mohammed Alhumud
- Jehad AlOrainy
- Abdulaziz Alshomar

Team leaders:

- **Raghad AlKhashan**
- **Amirah Aldakhilallah**
- **Mashal AbaAlkhail**
- **Nawaf Albhijan**

L31- Rheumatoid Arthritis

- **Definition:**
  - Autoimmune disease against the whole body (Joints mainly)
- **Pathogenesis:**
  - Synovitis → **Pannus → Erosions**
  - Pannus → T-cells and macrophages
  - Synovial fluid → Neutrophils
- **Clinical features:**
  - **Articular:**
    - **Symmetrical** arthritis of the small joints (**DIPJs are spared**)
    - **Deformities: Spindling**, "Z" deformity of the thumb, Swan neck (Hyperextension of PIPJ), Boutonniere (Flexion of PIPJ), ulnar deviation at the MCPJ and radial deviation at the wrist
    - ★ Cervical subaxial subluxation (**C1** and **C2**) (Do X-ray before surgery/intubation)
  - **Extraarticular:**
    - ★ **Felty syndrome:** RA + Splenomegaly + Neutropenia
    - **Caplan's syndrome:** RA + Lung nodules +Pneumoconiosis
    - **Scleritis** (cf. SpA)
    - Sjogren syndrome
    - Mononeuritis multiplex in case of **rheumatoid vasculitis**
    - Anemia of chronic disease (**Normocytic normochromic**)
    - CAD is the most common cause of death
    - Amyloidosis: Proteinuria + Edema + Carpal tunnel syndrome
- **Diagnosis:**
  - **Serology: RF** (IgM against Fc portion of IgG) and **Anti-CCP** (More specific) but both are not diagnostic
  - CBC (**Anemia** + **Thrombocytosis**)
  - ESR and CRP (Both will be high)
  - X-ray (**Erosions, periarticular osteopenia and subluxation**)
  - RFT and LFT for baseline before giving meds
  - ★ Aspiration of joint if you suspect Septic arthritis
    Note: **Suspect Septic if: Sudden + Monoarticular**; treat with aspiration and abx (Vanco or fluxo since Staph. Aureus is the most common)
- **Treatment:** (For all check CBC and LFT)
  - ***1st line:*** **NSAIDs (To relieve the pain) + MTX (To prevent progression)**
  - ***2nd line:*** NSAIDs + MTX + Leflunomide
  - ***3rd line:*** NSAIDs + MTX + Leflunomide + HCQ
  - ***Last resort:*** Anti-TNF (Check TB and fungal infxn)
    N.B. Use CS only for flare-ups or if NSAIDs are not working
  - ***Special cases:***
    - **If pregnant or mild non-erosive disease → HCQ (Check eye)**

L32- Scleroderma Spectrum Disease

Definition:

- A group of heterogeneous diseases that has a predominant feature and share other common features. They are rare, difficult to treat and associated with significant morbidity and mortality.

1. Scleroderma spectrum diseases

- **characterized by:**
  - **Skin thickening**
  - **Vasculopathy**
  - **Autoantibody**
- **Types of SSc**
  - **Diffuse:** (Diffuse Cutaneous Scleroderma (DcSSc) I 30% of cases)
    - Associated with **more internal organ involvement**
    - Has a **worse prognosis**
    - **Anti-topoisomerase** / RNA polymerase III antibodies.
  - **Limited:** (Limited Cutaneous Scleroderma (LcSSc) I 70% of cases)
    also known as CREST syndrome:
    - Calcinosis, Raynaud's phenomenon, Esophageal involvement, Sclerodactyly, Telangiectasia
    - Often more indolent (has a longer disease duration before diagnosis)
    - Has a **higher risk of pulmonary hypertension**
    - **Anti-centromere antibodies.**

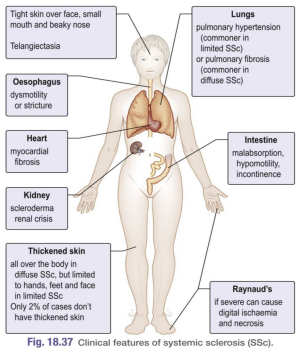


Fig. 18.37 Clinical features of systemic sclerosis (SSc).

- **AutoAntibodies in SSc**
  - **Anti-Scl-70 (topoisomerase) is associated with:**
    - **Diffuse** subset
    - The **development** of ILD
    - **Reduced** risk of PAH
  - **Anti-centromere is associated with:**
    - **limited** subset
    - **P**ulmonary **A**rterial **H**TN
    - **D**igital **u**lcer
  - **RNA polymerase III is associated with:**
    - **Scleroderma Renal Crisis**
    - **Malignancy** associated SSc
    - **Mortality.**

Involvements in SSc

- **Skin:**
  - Skin is the Largest and Most Important Organ in SSc
  - The **level of skin involvement** predicts **severe disease and mortality.**
  - ★ **SKIN INVOLVEMENT ALWAYS STARTS IN THE FINGERS AND TOES (distally) AND EXTENDS PROXIMALLY.**
  - **Treatment:** To prevent joint contracture and disability in the hands.
    - **Methotrexate:** Avoid it if the patient has interstitial lung disease or renal failure because of its toxic effect.
    - **Mycophenolate mofetil**
    - **Cyclophosphamide**
    - **Rituximab**
    - **Steroids:** High-dose corticosteroids is a **significant risk** factor for **Scleroderma renal crisis** and is best to be avoided in patients with DcSSc.

L32- Scleroderma Spectrum Disease

Involvements in SSc cont.

- **Skin: Raynaud's Phenomenon(RP) and Digital Ulcers(DU)**
  - 95% and 50% of SSc have RP and DU respectively, but **RP tends to occur years before the diagnosis of SSc** unlike DU that usually occur in the first 5 years after the development of the non-RP manifestation.
  - **Treatment in RP:**
    - **Calcium channel blockers (FIRST-LINE)**
    - If the patient is not responding you can give IV prostaglandins or even Phosphodiesterase inhibitors
    - **IV iloprost better than nifedipine.**
  - **Treatment in DU:**
    - **CCB has not role in Digital ulcer**
    - **Phosphodiesterase inhibitors & IV prostaglandins: Prevent** new ulcers and **Improve** (fasten) the healing.
    - **Endothelin receptor antagonist:** Only **prevents** new ulcers and **DO NOT** improve the healing.
- **Lungs: Interstitial lung disease:**
  - ★ Interstitial Lung Disease is the number ONE cause of mortality in patients with SSc.
  - ★ Common in patients with DcSSc who have topoisomerase 1 antibodies (Scl70)
  - High-resolution lung CT is the Gold standard.
  - ★ **Clinical findings in ILD:**
    - Tachypnea - Tachycardia - Cyanosis - Clubbing - Reduced chest expansion - Fine early inspiratory crackles
  - **Treated with** cyclophosphamide
- **Lungs: Pulmonary Arterial Hypertension:**
  - **PAH is defined as Pulmonary Arterial Pressure ≥ 25 mmHg** with a normal Pulmonary wedge pressure (≤ 15 mmHg.)
  - The **First** investigation to order is **echocardiography.**
  - The **Gold** diagnostic tool is **right sided heart catheterization.**
  - ★ **Clinical findings** (It is important to look at the lung and heart together)
    - Desaturation ● Tachycardia ● Palpable P2 ● Parasternal heave ● Loud 2nd heart sound ● Signs of right sided heart failure which include: JVD, lower limb edema and ascites. ● PFT may show isolated low DLCO
  - **Treatment:**
    - **Endothelin Receptor Antagonists:** Bosentan, Ambrisentan**,** Macitentan**,** Sitaxentan
- **Gastrointestinal System:** is the most common internal organ to be involved (95-99%) which includes:
  - **Mouth,** Esophagus (most common) , Stomach, Small bowel, Large bowel, Anorectal incontinence
- **Scleroderma Renal Crisis (SRC)**
  - Patients with SSc usually have low BP, once you see high BP suspect SRC.
  - Precipitating factors include: high dose steroids, cyclosporin & pregnancy.
  - **Best (and only) drug: Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)**
- **Others:**
  - **Arthritis:** similar to RA with erosions and joint destruction
  - **Myositis:** manifested by weakness with no pain and high muscle enzymes.
  - **Cardiac:** Myocardial fibrosis leading to conduction abnormalities, cardiomyopathy and accelerated coronary artery disease.

2. Sjogren's Syndrome

Definition:

- It is a systemic chronic inflammatory disorder characterized by **lymphocytic infiltrates** in **exocrine organs.** Especially the lacrimal and salivary glands. There is an association with HLA-88/DR3
- **Most individuals with Sjögren's syndrome present with sicca (dryness) symptoms, such as:**
  - **Xerophthalmia-** (dry eyes)**- Xerostomia** (dry mouth)**- Vaginal dryness- Parotid gland enlargement.**

Diagnosis criteria of primary Sjogren's Syndrome:

- **At least 4 of the criteria listed below (you MUST have number 1 or number 2)**
- The best initial test is Schirmer test
- the most accurate is a minor salivary gland (labial) biopsy.
- Best initial test on blood: SS-A and SS-B. These are also called "Ro" and "La" and are each present in about 65% of patients.
- Positive anti–SSA, This antibody is of particular interest because it can cross the placenta and cause congenital heart block

1	• Positive minor salivary gland biopsy findings showing lymphocytic infiltration.
2	• Positive anti–SSA[3] anti-sjogren syndrome A or anti–SSB anti-sjogren syndrome B antibody results
3	• Oral signs (sialogram, scintigraphy or sialometry findings)
4	• Ocular signs (Schirmer test)[2]
5	• Oral dryness
6	• Ocular dryness

Extraglandular manifestations of Sjogren's Syndrome:

- Arthritis - Myositis - Pancytopenia - Palpable purpura - **Renal tubular acidosis type 1** - **Severe unexplained Fatigue** - Raynaud phenomenon - Generalized osteoarthritis - Demyelinating disease **(Eg. Multiple sclerosis)** - interstitial lung disease - Interstitial nephritis - arthralgia

Treatment:

- The best initial therapy is to water the mouth.
- Parasympathomimetics (pilocarpine) **will increase the secretion of salivary and lacrimal glands.**

Complications:

- **SS patients are at risk of developing Non-hodgkin's B cell lymphoma 20 times more than the general population. Malignancy is the most common cause of death.**

3. Idiopathic inflammatory Myopathies

Definition:

- Are a group of autoimmune myopathies that are characterized by muscle weakness due to muscle inflammation and damage. they are **Mainly in the proximal muscles** but it can progress to peripheral muscles. and The onset is insidious and progressive.

Organ involvement:

- **Pharyngeal muscle** involvement can present as **dysphagia** and can lead to **aspiration pneumonia**.
- **Chest wall weakness** can present as **dyspnea** and lead to **type II respiratory failure.**
- Can affect the **heart** and lead to **cardiomyopathy**

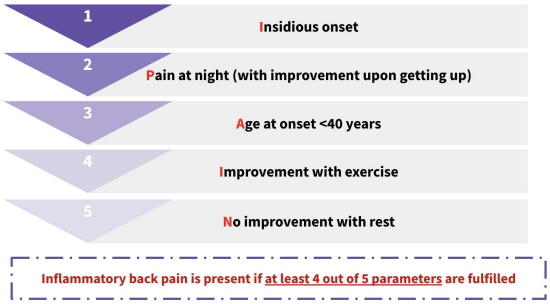
Investigations:

Muscle enzymes	CK, LD, AST, ALT, Aldolase. The **best initial test** is CPK and aldolase
MRI Muscle	Showing muscle edema
Muscle biopsy	Showing lymphocytic infiltration (Either CD4 or CD8, based on the subtype). Muscle biopsy is the **most accurate test** Establishing diagnosis and excluding other causes of myopathies.
EMG	Myopathic changes. Not very helpful
Autoantibodies	**Jo-1** the most common, occurs in around 40% of patients , Non-Jo-1 antibodies, Anti-SRP, Anti-Mi2
MOST IMPORTANT: RULE OUT OTHER CAUSES OF MYOPATHIES (Eg, hypothyroidism, hyperthyroidism, diabetes, cushing syndrome, Addison disease, statins ,etc)	

Treatment:

- **Steroids (Oral prednisolone is the treatment of choice)**
- Methotrexate
- Mycophenolate mofetil
- Azathioprine
- Rituximab
- **Intravenous immunoglobulins** if the patient has dysphagia or chest wall involvement (Heart, pharyngeal muscle, etc)

- **Introduction:**
  - **Low back pain:**
    - Can be inflammatory or mechanical
    - **IPAIN** criteria for inflammatory
  - **Definition of SpA:**
    - Seronegative spondyloarthropathies
    - Associated with HLA-B27
  - **Types:**
    - AS, nr-axSpA, IBD related, Juvenile, PsA and ReA



1. Ankylosing spondylitis:

- **Definition:**
  - Bilateral grade ≥2 Sacroiliitis on X-ray or unilateral grade 3 and 4 sacroiliitis
  - N.B. If changes are only seen on MRI then it's nr-axSpA
- **Clinical features:**
  - ASAS criteria; Low back pain for ≥ 3mo and age of onset < 45:
    - **Sacroiliitis + ≥ 1 SPPINE-ACHEE**
      OR
    - **+ve HLA-B27 + ≥ 2 SPPINE-ACE*E**
      ***Acute unilateral anterior uveitis** is the most common extra-articular feature, not related to disease activity
  - Kyphosis, loss of lordosis and reduced chest expansion

SpA features SPINE-ACHE

1) Dactylitis (**S**ausage digit)
2) **P**soriasis
3) **P**ositive family history for SpA
4) **I**nflammatory back pain
5) Good response to **N**SAIDS
6) **E**nthesitis (heel)
7) **A**rthritis
8) **C**rohn's/colitis
9) **H**LA-B27
10) Uveitis (**E**ye)
11) **E**levated CRP

- **Diagnosis:**
  - **Best initial:** X-Ray (Will show syndesmophytes and bamboo spine)
  - **Most accurate:** MRI
- **Treatment:**
  - ***1st line:*** NSAIDs
  - ***2nd line:*** TNF-inhibitors or IL-17 inhibitors

2. Psoriatic arthritis

- **Definition:**
  - Usually psoriatic lesions precede the arthritis (cf. AS) and it mainly involves the small joints (cf. AS)
  - Associated with nail lesions: Pitting, Oncholysis and ridging
  - Associated with Dactylitis
- **Patterns of arthritis:**
  - **Asymmetrical (after):** Oligoarthritis involving mainly small joints
  - **Symmetrical (Concurrent):** Involves small and large joints. Similar to RA.
  - **Ps Spondylitis (after):** Looks like AS but psoriatic lesions precede the arthritis
  - **DIP synovitis:** Only DIP joint is involved
  - **Arthritis mutilans:** Deforming erosive arthritis. Telescoping of skin.
- **Diagnosis:**
  - **Best initial:** X-ray (Will show pencil in cup)
  - **Most accurate:** MRI
- **Treatment:**
  - ***1st line:*** NSAIDs
  - ***2nd line:*** MTX
  - ***3rd line:*** Sulfasalazine
  - ***4th line:*** TNF-inhibitors or IL-17 inhibitors
    N.B. (If Ps Spondylitis use TNF-inhibitors or IL-17 inhibitors as 2nd line)

3. Reactive arthritis

- **Definition:**
  - STERILE arthritis following GI/GU infection (usually after 2 weeks)
  - Formerly known as Reiter's syndrome: Can't see, can't pee, can't climb a tree
- **Etiology:**
  - **GI:** Shigella, Salmonella, C.diff, Campylobacter and Yersinia
  - **GU:** Chlamydia
- **Clinical features:**
  - Asymmetrical oligoarthritis and Achilles enthesitis
  - Circinate balanitis: Superficial erosions on glans penis
  - Keratoderma blennorrhagica: Yellow-brown papules on palms and sole of foot
- **Diagnosis: (Usually clinical)**
  - Tap joint: Sterile with high neutrophils
  - Radiology: Similar to PsA
- **Treatment:**
  - ***1st line:*** NSAIDs
  - ***2nd line:*** MTX or Sulfasalazine
  - ***3rd line:*** TNF-inhibitors
  - **Abx against chlamydia:** Doxycycline/Azithromycin
    N.B. Don't use abx unless an organism has been identified

L34- SLE

Definition:

- Chronic, multisystem inflammatory disease characterized by autoantibodies directed against self-antigens, immune complex formation, and immune dysregulation resulting in damage to essentially any organ.

Pathophysiology: Disturbances in the immune system:

- **High ratio of CD4+ to CD8+ T cells.**
- **Defects in immune cell tolerance leading to:** Production of **autoantibodies targeting** antigens located in **nuclei**, **cytoplasm**, on cell surfaces, and in plasma proteins
- **Autoantibodies**

Etiology: Specific cause(s) of SLE is unknown. Multiple factors play a role in the etiology of SLE:

- Environmental: **Ultraviolet light**, viruses (e.g. **EBV**), drugs cause or exacerbate, silica dust, smoking.
- Genetics predisposition : **HLA-DR2** and **HLA-DR3** and other HLA genes occur more often in SLE than in the general population.
- **Female to male rations and Hormonal factors: Age at onset :**
  - ➔ 65%: between **16 and 55 (Reproductive age)**.
  - ➔ 20%: before age 16.
  - ➔ 15%: after age 55 .
- Higher prevalence in men with **Klinefelter disease**, their extra X chromosome increases their susceptibility.

Organ involvement:

- **Joints 90%**
- **Pleuropericardial 60%**
- **Skin**
- **Kidney 50%**
- **Raynaud's 20%**
- **CNS 15%**
- **Mucous membrane 15%**

Clinical presentation and diagnostic criteria:

ANA is needed to diagnose: found in 95%-99% of cases. A negative ANA is extremely sensitive for SLE. You need to have **at least 4** of the following: (the more you get the more definite the diagnosis is) :

- Malar rash : tending to spare the nasolabial folds.
- Discoid rash : Erythematous raised patches. Chronic, affect deeper layers.
- **Photosensitivity**
- **Oral ulcers : painless**
- **Arthritis: Nonerosive** (but maybe deforming) arthritis involving 2 or more peripheral joints, usually symmetrical. characterized by tenderness, swelling, or effusion.
- **Serositis : A. Pleuritis B. Pericarditis C. Peritonitis**
- **Renal disorder : A.Persistent proteinuria** (>0.5 g/day) **B. Cellular casts**
- **Neurologic disorder : A . Psychosis or Seizures B. Cerebral lupus feature:** visual hallucination, chorea
- Hemolytic disorder : A. **Hemolytic anemia** **B. Neutropenia C. Lymphopenia D. Thrombocytopenia E.Leukopenia**
- **Immunologic disorder either: A. +ve antiphospholipid antibodies. B. Anti-DNA:** antibody to native DNA in abnormal titer Highly associated with lupus nephritis,+ it correlates with disease activity so it's used for **monitoring**
- **Antinuclear antibody (ANA)**

Clinical features:

- **Bullous rash**
- **Subacute cutaneous lupus erythematosus:** associated with **Anti-SSA/RO** & neonatal lupus. **leads to complete heart block** in the fetus (2%)
- **Chronic discoid rash Discoid scarring alopecia** (Irreversible)
- **Alopecia :** usually non scarring, goes back to normal once you treat the patient.
- **Externally not distinguishable from RA :** X-ray shows **non erosive** correctable deformity
- **Lupus in the lung capillaries (Emergency):** Pulmonary alveolar hemorrhage (mortality is 50%)
- Other symptoms: constitutional symptoms: **Fever** → one of the DDx of fever with unknown origin is SLE

Investigations:

- Blood count :
  - Normochromic, normocytic anaemia or autoimmune hemolytic anemia
  - Neutropenia
  - Lymphopenia
  - leucopenia
  - thrombocytopenia
- ESR and CRP : ESR: **A raised ESR, leukopenia and lymphopenia are typical of active SLE**
- **Urea and creatinine.**
- **Serum :**
  - **Complement C3 and C4 levels: reduced** in active disease
  - **Autoantibodies:**
    a. **ANA:** Sensitive but not specific
    b. **Anti-ds DNA** (in 70%): highly specific (but not sensitive)
    c. **Anti-Smith** (in 30%): very specific (but not sensitive)
    d. **Antiphospholipid antibodies** (in 25% to 40%)
    e. **Antihistone** (in 70%) are present in >95% of cases of **drug-induced lupus**.

Drug induced lupus:

- Nephritis and CNS not common.
- No anti-native DNA or hypocomplementemia.
- Resolution on **discontinuation of drug**.
- **Drugs with definite association with lupus erythematosus :**
  - Chlorpromazine(antipsychotic)
  - **Methyldopa** (antihypertensive)
  - **Hydralazine**(antihypertensive)
  - **Procainamide** (antiarrhythmic)
  - Isoniazid (antibiotic)
  - Quinidine

Treatment of SLE:

- **Mild to moderate disease:**
  - **NSAIDS**
  - **hydroxychloroquine**
- **Life-threatening disease :** for the treatment of **renal, CNS, and cardiac involvement** or flares.
  - **High-dose corticosteroids and immunosuppressants**
  - immunosuppressant drugs
    - **Cyclophosphamide** we **try to avoid in patients in productive age**. If we need to give it, it is given at lower doses, then switch to mycophenolate.
    - **Mycophenolate mofetil**:
- **General considerations:**
  - Avoid UV light and sun (sunscreening)
  - Antimalarial (Hydroxychloroquine and chloroquine) to prevent **relapses**. (For those who already got Lupus to prevent relapses, not just have +ve ANA)

Pregnancy and SLE:

Recurrent miscarriages can occur, **especially in women with anti-phospholipid antibodies**.

Prognosis:

- Poor prognostic factors for survival in SLE include:
  - Renal disease
  - Hypertension
  - Central nervous system (CNS) disease
  - presence of anti phospholipids antibodies: increase the risk for thrombosis.
    - Treatment: Warfarin (DO NOT USE NOAC)

HIV Structure

subgroup of retroviruses, and it is an RNA viruses that replicate via a DNA intermediate.
It is made of:

1. The core: contain the genetic material [RNA] and Reverse transcriptase [enzyme]
2. The capsid: outer protein coat. (p24)
3. Lipid envelope (env): It's derived from infected cell, containing numerous external spikes formed by two major envelope proteins:
   a. The external gp120 which attaches to host CD4+ T-cell.
   b. The transmembrane gp41
4. Polymerase (pol)

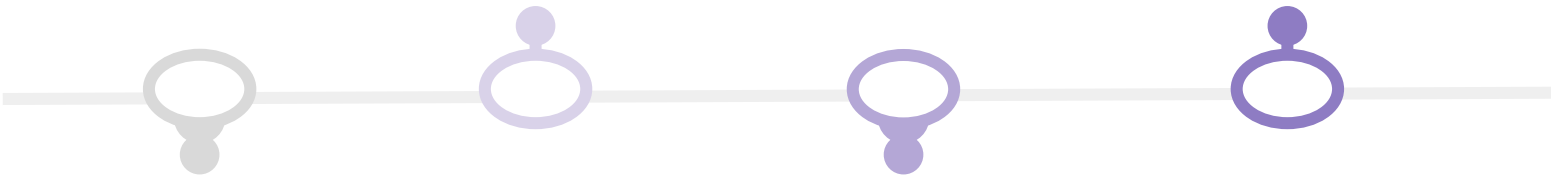
Genetic susceptibility

CCR5 (delta) 32 homozygotes genotype: people who inherited the Delta 32 mutation, resulting in the genetic deletion of a portion of the CCR5 gene are **highly resistant to HIV infection.**

Routes of Transmission

Mother to child
Can occur in utero (30%), although the majority of infections takes place perinatally (60%). It also can transmitted through breast milk (10%)
one-third of their babies become infected.

Contaminated needles
share needles and syringes. Health care workers with a needle-stick exposure are at high risk as well.



Sexual intercourse
heterosexual and homosexual

Blood, blood products

What factors increase the risk of HIV transmission?

1. High viral load. (Acutely infected or chronically untreated patient)
2. Certain sexual behaviours.(MSM is more)
3. Presence of ulcerative sexually transmitted infections.
4. lack of circumcision.
5. Certain other host and genetic factors.

Complications of HIV infection

1. Pneumocystis jirovecii Pneumonia :

One of the leading causes of opportunistic infections among persons with HIV and low CD4 cell counts (<200 cell/mm3). It causes lower respiratory tract infection, Occurs in those who are unaware of their HIV diagnoses or are not receiving medical care.

- Pneumocystis is currently recognized as a fungus (atypical fungi).
- X-ray: typically shows bilateral perihilar interstitial infiltrates.
- Definitive diagnosis of PCP requires visualization of the cystic or trophic forms in respiratory secretions by methenamine silver stain
- Treatment: Trimethoprim-sulfamethoxazole.

i 12.9 CD4 count and risk of common HIV-associated diseases

<500 cells/mm³	
• Tuberculosis	• Kaposi's sarcoma
• Bacterial pneumonia	• Non-Hodgkin lymphoma
• Herpes zoster	• HIV-associated idiopathic thrombocytopenic purpura
• Oropharyngeal candidiasis	
• Non-typhoid salmonellosis	
<200 cells/mm³	
• *Pneumocystis jirovecii* pneumonia	• HIV wasting syndrome
• Chronic herpes simplex ulcers	• HIV-associated dementia
• Oesophageal candidiasis	• Peripheral neuropathy
• *Cystoisospora belli* (syn. *Isospora belli*) diarrhoea	• Endemic mycoses
<100 cells/mm	
• Cerebral toxoplasmosis	• Cytomegalovirus
• Cryptococcal meningitis	• Disseminated *Mycobacterium avium* complex (MAC)
• Cryptosporidiosis and microsporidiosis	• Progressive multifocal leucoencephalopathy
• Primary CNS lymphoma	

2. Malignancy (AIDS-defining cancers):

a) Kaposi sarcoma

- associated with human herpesvirus 8 (HHV-8).
- (CD4 <500 cells/mm3).
- Diagnosis: Skin biopsy: spindle-shaped cells, leukocyte infiltration, and angiogenesis
- Management: decrease Incidence with use of antiretroviral therapy (ART).

b) Non-Hodgkin lymphoma

i) EBV related

c) Cervical cancer.

i) Related to HPV.

Diagnosis

Whom to test?

1. **Symptoms of HIV infection:**Signs and symptoms of acute or chronic HIV infection should be tested. Testing for HIV RNA may be needed.
2. **Possible HIV exposure:** Patients after a known high-risk exposure to HIV (eg, sexual or percutaneous)
3. **Patient with sexually transmitted disease (STD).**
4. **Pregnant women** should be tested for HIV early in each pregnancy.

Positive result with **Third-(HIV- antibody only**, time to positivity 20-30 days**)** and/or **Fourth-generation (HIV antigen and antibody,** time to positivity 15-20 days**)** HIV serologic assays **should be confirmed by** confirmatory **HIV-1/HIV-2 antibody differentiation immunoassay**.

What is the definition of Acquired Immunodeficiency syndrome (AIDS)?

1. It is defined by a loss of CD4 T lymphocytes (< 200 cell) OR
2. The occurrence of opportunistic infections or cancers in HIV infected Patient.

Treatment

- Current ART does not cure HIV, only highly suppresses viral replication.
-Combination antiretroviral therapy (ART) declines in morbidity and mortality among persons with HIV.

most countries start treatment if:

1- CD4 count ≤350 : Initiating ART results in a significant decline in the risk of AIDS-related morbidity and mortality
2-CD4 count <200 cells [AIDS] : ART improves survival and delays disease progression.

Treatment is initiated with three drugs: two NRTIs in combination, with a third agent - either an NNRTI, a boosted PI or an integrase inhibitor.

Drugs

1. **Reverse transcriptase inhibitors (-INE,-VIR)**
   a. Nucleoside Analogue RTI (NRTI): Abacavir (ABC), Emtricitabine(FTC) , Lamivudine(3TC) , Tenofovir
   b. Non-nucleoside RTI (NNRTI): Delavirdine , Efavirenz , Nevirapine.
2. **Protease inhibitors (-NAVIR):** Atazanavir, Darunavir
3. **Integrase inhibitors:** Raltegravir, Dolutegravir

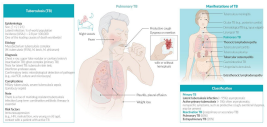
Prevention

Use of ARVs for prevention	
Secondary prevention benefits of ART • Several studies confirmed that if an HIV-positive person is taking ART and is virally suppressed they do not transmit HIV to their uninfected sexual.	
Pre-exposure prophylaxis for HIV-negative partner	• Oral PrEP of HIV is the daily use of ARVs by HIV-negative people to protect themselves from high-risk sexual and needle-sharing practices with potentially HIV-infected contacts. Its effective in reducing HIV transmission.
Post-exposure prophylaxis	• **Indicated in case of:** ○ Sexual contact (unprotected) ○ Health care associated percutaneous exposure. (Needle-stick) • PEP may be useful up to 72 hours after possible exposure. • PEP is **not recommended when care is sought > 72 hours after potential exposure.** • PEP is given for 1 month as a combination therapy

How to eliminate Mother to child transmission?

1. Effective antiretroviral therapy (ART)
2. Formula feeding

HIV-positive women are advised against breast-feeding, which doubles the risk of vertical transmission.



L36- Tuberculosis

Overview

- Tuberculosis is a bacterial infection caused by **Mycobacterium tuberculosis**
  - **Mycobacteria are acid-fast bacilli (AFB)—considered slow growing but hardy organisms.**

Transmission

- By inhalation of **aerosolized droplets** containing the active organism from a person with active TB.
- After exposure to TB the patient will either present with an active TB or will just remain in a dormant latent phase of TB. Whether the patient had the infection or developed latent TB, **TST or IGRA will be positive.**

Risk factors

For TB infection:
- Exposure to TB case & HCWs
- Homlessness or imprisonment
- From TB endemic areas
- Injection drug users

For Progression to TB disease:
- **Recent infection (<2 years)**
- **HIV-positive patients**
- Immunosuppression (anti TNF-a)
- ESDR - DM - Silicosis
- CXR showing prior TB
- Malnoureshment (intestinal bypass)
- Cancer (Hodgkin/Leukemia)

Clinical Presentation

General symptoms: - Fever - Sweats - Weight loss - Malaise - Decreased appetite

Pulmonary TB:
- Cough - Purulent sputum - Haemoptysis in cases of cavitation - SOB
- Subacute in onset, but can be acute in immunocompromised patients.

Extrapulmonary TB:
- TB can affect any organ: (**TB lymphadenitis** (25%), Pleural TB, Skeletal TB, **TB meningitis**, GI & GU).
- It is important to obtain clinical specimens from the site affected.

Disseminated (Miliary) TB
- hematogenous spread TB.
- Presents with acute sepsis-like syndrome esp. in immunocompromised patients.
- Mostly nonspecific, could include lymphadenopathy or hepatosplenomegaly.

Diagnosis: - **blood culture** and resp. specimens - CXR: multiple small nodules

Diagnosis

Smear microscopy:
- 3 Specimens.
- ↓ Specificity and Sensitivity.

Rapid MTB PCR:
- ↑ **Specificity**, shows Rifampicin resistance.

PPD & IGRA:
- Don't distinguish latent from active.
- **IGRA isn't affected by prior BCG.**
- **IGRA False +ve:**
- **M. Kansasii - M. Marinum.**

Histopathology:
- Caseating granuloma

Culture:
- **Highest Sensitivity**
- **GOLD STANDARD**

Chest Imaging (CXR):
Apical cavity ± lymphadenopathy.

Treatment & Prevention

First line therapy: (RIPE)
Induction: (2 months) **> ADR**
- **R**ifampin **(enzyme inducer)**
- **I**soniazid (**I**NH) **> Per. Neuropathy**
- **P**yrazinamide **> hyperuricaemia**
- **E**thambutol **> Optic Neuritis**

Continuation:
- **I**NH & **R**ifampin (4 months)

Treatment for latent TB (i.e., +PPD skin test):
- **Rifampin daily for 4 months** or INH daily for 9 months
- **Active TB has been excluded FIRST (negative CXR, sputum, or both).**

Extend treatment in case:
Pulmonary TB is persistent (CXR/culture) (9m total)
CNS TB (9-12m total)
Bone and Joint TB (6-9m total)

Prevention:
BCG Vaccine.

HIV & TB

IMP:
With immunosuppression:
- **Smear -ve Pulmonary TB**
- **Extrapulmonary TB (CNS, miliary)**

Rifampin is replaced by Refabutin.

When to start ART

CD4< 50:
Within 2 weeks of TB treatment

CD4> 50
Within 8 weeks of TB treatment

HIV +ve pregnant w/ active TB:
As soon as feasible

TB meningitis:
After 8 weeks of TB treatment

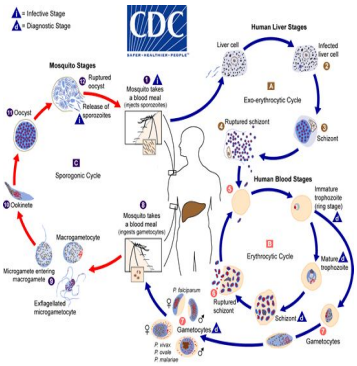
L37- Malaria & Travel Medicine

◄ Definition

- Malaria is a protozoal infection that infects hepatocytes and RBCs.
- Most commonly caused by **P.falciparum** and P.vivax.
- It can be transmitted through human to human by anopheles mosquitoes, blood transfusion, contaminated needles and congenital.
- **Stable transmission: sub- Saharan Africa,**The bulk of the mortality is seen in **children**,
- **Unstable transmission:** occurs when there is **erratic, seasonal or low- level transmission** (e.g. in the Sahel belt) . Little protective immunity develops and symptomatic malaria occurs at all ages.

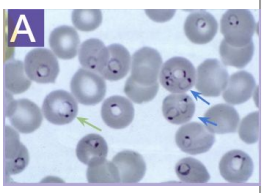
◄ Life cycle

- Carried by **female anopheles mosquito**. It injects the body with **sporozoites** that will reach the hepatocytes and form **Exoerythrocytic Schizonts**.
- These schizonts will rupture releasing merozoites → that will enter the erythrocytes forming **immature trophozoites** (ring stage)
- Then it will either develop into **mature trophozoite** → and again forming **erythrocytic Schizont** that will release merozoites into the bloodstream causing the **clinical attack**.
- Or the immature trophozoite develop to gametocytes.



Plasmodium Falciparum

- **Resistant** to many antimalarial drugs.
- ★ Causes most **morbidity and mortality.**
- Infects **mature and young erythrocytes**. The surface of erythrocytes infected with late stage **trophozoites** or schizonts is altered so they stick to endothelial cells in various tissues (cytoadherence) causing multi-organ failure.
- The gametocytes are characteristically crescent-shaped
- **Pic A:** rings in peripheral blood thin film of P.Falc showing double dotted ring and multiple parasites invading one RBC. These findings are **characteristic for P.Falciparum.**



P.vivax	P.ovale	P.malariae
- Only infect Duffy +ve reticulocytes. - Schuffner's dots.	- Most of the biological and **clinical features are identical** to P.vivax. - Can infect Duffy -ve reticulocytes.	- P. malariae can survive for a very long time in the peripheral blood (10 years or more) at a very low level of parasitaemia

◄ Malaria Paroxysms

- Paroxysms associated with **synchrony of merozoite release.**
- Cold skin (1-2hr) → Hot skin (several hrs) → sweating and fatigue.
- **Between paroxysms temperature is normal and patient feels well and asymptomatic.**
- **Terian** (every 48hr) → P.vivax and P.ovale.
- **Quartan** (every 72hr) → P.malariae.
- **irregular**→ P.falciparum.

◄ Clinical presentation

- Hx of travel to malaria endemic area (1 year for P.falciparum and up to 10 years to P.malariae).
- **Symptoms**: Fever, **jaundice** (common in p.falc) , sweats, headache, cough diarrhea, dark urine.
- **Signs**: Splenomegaly is the most common.

◄ Complications

- **Cerebral malaria (Pf):**
  - ★ Risk factor for poor prognosis: **high bilirubin, high creatinine and high lactase**. if these were normal → no end organ damage.
- **Hypoglycemia -** quinn leads to insulin release.
- **Risk acute respiratory syndrome (Pf).**
- **Acute renal failure (Pf).**
- **Malaria with pregnancy will lead to abortion.**

WHO Criteria – Severe Malaria

History of recent possible exposure and no other recognized pathology. **EITHER** Asexual forms of (Pf) on blood smear.

AND

Any one or more of the following 11 features:

01 Impaired consciousness or coma.
02 Severe normocytic anemia.
03 Renal failure.
04 Pulmonary edema or adult respiratory distress syndrome (ARDS).
05 Hypoglycemia.
06 Circulatory collapse, shock
07 Spontaneous bleeding/disseminated intravascular coagulation.
08 Repeated generalized convulsions.
09 Acidemia/acidosis.
10 Hemoglobinuria.
11 Parasitemia of > 5% (> 250 000/microlitre) in non-immune individuals.

◄ Diagnosis

- **Thin and thick films:** A thin film is essential to confirm the diagnosis, to identify the species of parasite and, in P. falciparum infections, to quantify the parasite load (by counting the percentage of infected erythrocytes).
  - **Pf** → only **ring stage** asexual parasite and **gametocytes** can be seen, while RBC mature (trophozoite and schizont) stage sequestered in the peripheral microvasculature and not circulating.
  - **P.vivax & P.ovale** → **all asexual erthrocytic stages** can be seen.
- **DDx of acute ill patient:**
  - Not P.malariae because it's chronic infection.

Thin and Thick films[1]	Urea and Creatinine	ABG
CBC, Coagulation profile	LFT, Bilirubin	CXR
Random Blood glucose	Lactic acid	Urine analysis

Findings	P. Falciparum	P. Vivax & P. Ovale
Multiple infected RBCs	Common	Rare
Mature (trophozoite & schizont) parasites	Absent	Common
RBC enlargement with later parasite stages	Absent	Common

◄ Management

- Ask lab about: species and **percent parasitemia (>1% → Pf)**.
- Complicated or uncomplicated?
- ★ **Drug of choice** is Artesunate based combination therapy (ACT), P. falciparum is now resistant to chloroquine and sulfadoxine-pyrimethamine (Fansidar) world-wide, so an ACT is recommended
- Consider admission to hospital (especially for falciparum) at least
- observe tolerance of meds in ER..

★ P.falciparum			Non P.falciparum
Uncomplicated	**Complicated "severe malaria"**	**Pregnant women**	
- **ACT** for 3 days. - OR oral quinine + doxycycline or clindamycin for 7 days.	- **IV Artesunate** up to 7 days. - OR IV quinine up to 7 days. - OR IM Artesunate up to 7 days.	Artesunate is the drug of choice in all trimesters.	- **Chloroquine** (base). - **Primaquine** for 14 days in vivax and ovale after treatment of acute infection use to **eradicate liver parasites**; **G6PD must be measured** before primaquine is given.

◄ Drug toxicity

- **Quinine** → Hypoglycemia and arrhythmia .
- **Mefloquine** → Neuropsychiatric symptoms.
- **Chloroquine** → irreversible retinopathy.

Chemoprophylaxis[1]:

- **Start 2 days pre-travel, continue 7 days after return:**
  - → Atovaquone/ proguanil[2] (Malarone): 1 tab/d (250 mg atovaquone /100 mg proguanil)
- **One or 2 weeks pre-travel, continue 4 weeks after return:** less preferred
  - ★ Mefloquine 250 mg once/wk.
  - → Doxycycline 100 mg daily.
  - → Primaquine 30 mg base daily.
  - → Chloroquine[3] sensitive areas: 500 mg (300 mg base) : once/wk.

1. Choice of regimen is determined by area to be visited, length of stay, level of malaria transmission, level of drug resistance, presence of underlying disease in the traveler concomitant medication taken.
2. **Pregnant** and lactating women may take **proguanil** or **chloroquine** safely. Avoid Malarone in pregnancy.
3. **Chloroquine** should not be taken continuously as a prophylactic for more than 5 years without regular ophthalmic examination, as it may cause **irreversible retinopathy**.

Source of infection

- Endogenous sources: skin, nose, mouth, GI tract, or vagina
- Exogenous sources: health care workers (HCW), visitors, patient care equipment, medical devices, or the healthcare environment.

FIRST: Catheter-Associated Urinary Tract Infections

- **Causes**: Indwelling urinary catheter, Urinary invasive procedures.
- **Risk factors**: Advanced age, Diabetes mellitus, Pregnancy, Urolithiasis, Severe underlying disease.
- **Pathogenesis:**
  - Endogenous (meatal, rectal, or vaginal).
  - Exogenous; usually via contaminated hands of HCW during catheter insertion or manipulation of the collecting system.
  - (Formation of bio films by urinary pathogens which lead to resistance of antimicrobials and host defenses, you must remove catheter for cure).
- **Diagnostic criteria:**
  - Fever1 (38.0C or above), urgency, frequency, dysuria, or suprapubic tenderness.
  - Positive urine culture, that is more than 105 CFU per ml, with no more than 2 species of microorganisms.
  - A positive culture of a urinary catheter tip is not an acceptable laboratory test to diagnose UTI.

SECOND: Surgical site infection

- **causes:**
  - Inadequate antibiotic prophylaxis
  - Incorrect surgical skin preparation
  - Inappropriate wound care
- **Risk factors:** surgical duration, type of surgery, type of wound, Improper surgical aseptic preparation, poor glucose control, Malnutrition, Immunodeficiency, Hypothermia, Lack of training and supervision.
- **Causative organisms:** Staph. Aureus (30%) → most common, followed by coagulase -ve staph (13.7)
- **Surgical Wound Classification**
- **Clean:** Uninfected, no inflammation, Resp, GI, GU tracts not entered, Closed primarily.
  Examples: lap, mastectomy, neck dissection, thyroid, vascular, hernia,splenectomy.
- **Clean-contaminated:** Resp, GI, GU tracts entered but controlled, No unusual contamination
  Examples: Chole, SBR, Whipple, liver txp,gastric surgery, bronch, colon surgery, cholecystectomy.
- **Contaminated:** pen, fresh, accidental wounds, Major break in sterile technique, Gross Spillage from GI tract, Acute non purulent inflammation.
  Examples: Inflamed appendix, bile spillage in chole, diverticulitis, Rectal surgery, penetrating wounds.
- **Dirty:** Old traumatic wounds, devitalized tissue, Existing infection or perforation, Organisms present BEFORE procedure.
  Examples: Abscess I&D, perforated bowel, peritonitis, wound debridement, positive cultures pre-op.

Superficial vs deep surgical site infection

- **Superficial SSI**: within **30 days,** involves only **skin and subcutaneous tissue** of the incision
  - **Signs:** Purulent drainage from the superficial incision, pain or tenderness, localized swelling, redness, or heat, lack of systemic symptoms (e.g. fever). A -ve culture does not rule it out
- **Deep SSI**: **within 30 days if no implant is left in place** or **within 1 year if implant is in place and the infection appears to be related to the operative procedure**, Involves **deep soft tissues** (e.g. fascial and muscle layers) of the incision,
  - Clinically may have abscess and fever.

SSI Epidemiology

- Modifiable Risk Factors: Antimicrobial prophylaxis(Inappropriate choice, Improper timing, Inadequate dose based on body mass index, procedures >3h).
- Skin or site preparation ineffective.
- Colorectal procedures; Inadequate bowel prep/antibiotics.
- Inadequate wound dressing protocol.
- Improper glucose control.
- Colonization with preexisting microorganisms.

SSI Prevention strategies:

- **Preoperative Measures:** Administer antimicrobial prophylaxis in accordance with evidence based standards and guidelines: Administer within **30-45 minutes to incision** (**1-2hr for vancomycin and fluoroquinolones**), Select appropriate agents on basis of: Surgical procedure, Most common SSI pathogens for the procedure, Published recommendations, Consider Redosing in long procedures (>3hrs) and increasing dose in obese patients.
- **Nasal screen and decolonize only Staphylococcus aureus (MRSA) carriers** undergoing: Elective cardiac surgery, Orthopaedic surgery, Neurosurgery procedures with implants, Using preoperative mupirocin ointment therapy known as decolonisation.

THIRD: Central line Associated Bloodstream Infections

- Direct: in IJV or femoral or subclavian veins.
- Tunneled: for dialysis and chemotherapy.
- Laboratory-confirmed bloodstream infection by a positive blood culture that's not secondary to any infection.
- Develops at least after 48 hours of a central line placement
- The most common site is the **femoral central lines**

CLABSI Microorganisms

1. **Gram +ve cocci**: **Coagulase -ve staphylococcus** **(most common)**, Enterococci, Staph. aureus.
2. **Gram -ve bacilli:** Klebsiella pneumoniae, E.coli, Enterobacter spp, Pseudomonas aeruginosa, Acinetobacter baumanii.

CLABSI Treatment

- Removal of central line
- Antimicrobial therapy: Type and duration depends on culture results, type of organism, complicated disease (Vancomycin, cloxacillin, cefazolin, piperacillin/ tazobactam).

CLABSI prevention

1. **Prevention Guidelines During Insertion:**
   - Hand hygiene before wearing gloves
   - Strict aseptic technique by maximal sterile barrier precautions including a full-body drape
   - Use of 2% chlorhexidine skin preparations for disinfecting/ cleaning skin before insertion
   - Ultrasound guidance by an experienced personnel and reduce the number of attempts
   - Avoid the femoral vein, prefer the subclavian vein
   - Promptly remove any central line that is no longer required
   - Replace central lines placed during an emergency (asepsis not assured) as soon as possible or at least within 48 hours
   - Use a checklist
2. **Prevention Guidelines During Maintenance:**
   - Disinfect catheter hubs injection ports, and connections before accessing line
   - Replace administration sets other than sets used for lipids or blood products every 96 hours
   - Assess the need for the central line daily

Pathogenesis and risk factors for ventilator Associated Pneumonia (VAP)

- Aspiration of secretions
- Colonization of the aerodigestive tract
- Use of contaminated equipment

VAP prevention bundle

1. **Prevent Aspiration of Secretions:**
   - Maintain elevation of head of bed (HOB) 30-45 degrees
   - Avoid gastric over distention
   - Avoid unplanned extubation and re-intubation
   - Use cuffed endotracheal tube with in-line or subglottic suctioning
   - Encourage early mobilization of patients with physical/occupational therapy
2. **Reduce Colonization of Airway and Digestive Tract:**
   - Use cuffed Endotracheal Tube with inline or subglottic suctioning
     - Minimizes secretions above cuff; prevents contamination of lower airway.
   - Avoid acid suppressive therapy for patients not at high risk for stress ulcer or stress gastritis
     - Increases colonization of the digestive tract.
3. **Reduce Duration of Ventilation:**
   - Conduct "sedation vacations"
   - Assess readiness to wean from vent daily
   - Conduct spontaneous breathing trials
4. **Prevent exposure to contaminated equipment by using closed-circuit for ventilator.**

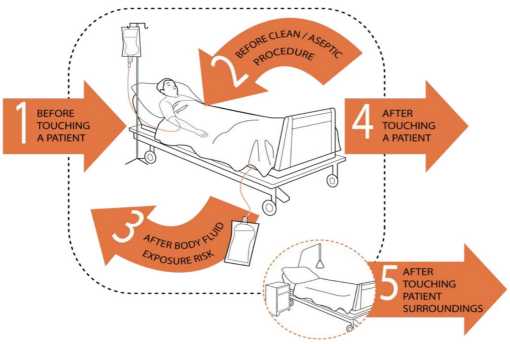
Modes of transmission: A microorganism may be spread by a single or multiple routes(Contact, direct or indirect, Droplet, Airborne, Vector-borne (usually arthropod) and, food-borne and waterborne, medications e.g., contaminated IV fluids).
Hand transmission: Hands are the most common vehicle to transmit healthcare associated pathogens.

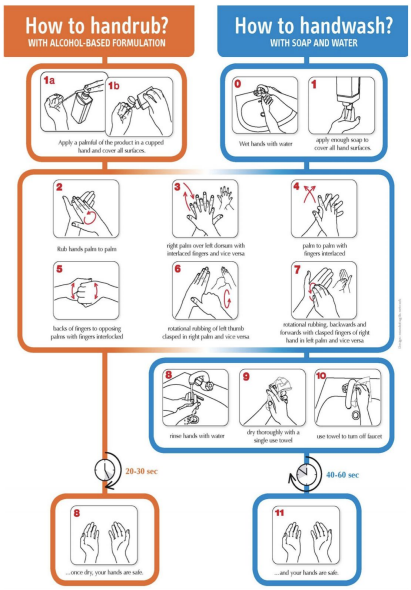
Five Moments of Hand Hygiene

How to Clean Your Hands?

1. Handrubbing with alcohol-based handrub is the preferred routine method of hand hygiene if hands are not visibly soiled

2. Handwashing with soap and water – essential when hands are visibly dirty or visibly soiled (following exposure to body fluids) and after certain diseases e.g. C. difficile as they are spore forming bacteria that don't get disinfected by alcohol.





Types of Isolation Precautions

- Standard precautions.
- Transmission-based precautions:(Contact isolation, Droplet isolation, Airborne isolation).

Contact Precautions

- C. difficile, MRSA, VRE, ESBL, CRE and MDR GNR.
- Limit patient movement.
- Private/single room or cohort with patients with same infection.
- Wear **disposable gown and gloves** when entering the patient room.
- Remove and discard used gown and gloves inside the patient room.
- Wash hands immediately after leaving the patient room.
- Use dedicated equipment if possible (e.g., stethoscope)

Droplet Precautions

- E.g.MERS-CoV, SARS-CoV-2, influenza.
- A private/single room or cohort with patient with active infection with same microorganism.
- Use a **mask** when entering the room especially within 3 feet of patient.
- Limit movement and transport of the patient. Use a mask on the patient if they need to be moved and follow respiratory hygiene/cough etiquette.

Airborne Precautions

- **Tuberculosis,** measles, varicella, MERS-CoV (severe), COVID-19 or AGP.
- Place the patient in an airborne infection isolation room (AIIR)
- **Negative Pressure** should be monitored with visible indicator
- Use of respiratory protection (e.g., fit tested **N95 respirator**) or powered air-purifying respirator (PAPR) when entering the room
- Limit movement and transport of the patient.
- Use a mask on the patient if they need to be moved.
- Keep patient room door closed, do not open anteroom door till other door closed

Serologies and Vaccination

- HBSAB titre (above 10)
- VZV
- MMR
- Td
- Seasonal Influenza Vaccine
- COVID-19 vaccine

◄ Summary of precautions for patients with COVID-19

Personal Protective Equipment	Close patient contact (within 2m)	Enter room but no contact with patient or environment	Cleaning room/area (Domestic staff)	★ Aerosol generating procedures
Gown	✅	❌	✅	❌
Surgical mask	✅	✅	✅	❌
Long sleeved disposable gown	❌	❌	❌	✅
Fit Tested N95 respirator	❌	❌	❌	✅
Eye protection (goggles, face shield)	Risk assess	❌	❌	✅
Gloves	✅	❌	✅	✅

L40- Endemic infections in The middle east

	Typhoid fever	Brucellosis	Dengue	Rift Valley
Introduction/ Epidemiology	-Severe **systemic illness with fever and abdominal pain** -Caused by **Salmonella typhi** and paratyphi -Common in children and young adults	-**Systemic febrile illness** **-(Brucella) Aerobic intracellular gram negative coccobacilli** -Mostly **Mediterranean basin and Arabic peninsula** **-uncommon in infants**	-Dengue fever and Hemorrhagic fever **caused by dengue virus** -Mosquito borne (**Aedes aegypti**) - in **Tropical and subtropical areas**	-**Acute fever** causing **zoonotic and human disease** -Phlebovirus, **transmitted by mosquitoes or infected mammals**
Pathogenesis	1-Organism enters the blood through **fecal oral route** 2- **multiply in mesenteric lymph nodes** 3- infect the **reticuloendothelial system** (spleen, liver, bone marrow)	-**Zoonotic infection** transmitted through **contact with fluids** (Aerosols inhalation, **unpasteurized dairy**, undercooked meat, lab workers) - survives phagocytosis - replication in reticuloendothelial system and other organs	**Clinical features:** 1-**Dengue fever:** -Incubation period (3-14 days) -Symptoms appear (4-7 days after bite) -acute febrile illness with **fever** and 2 symptoms of: **(**Headache, **retro-orbital pain,** myalgia, arthralgia, rash) 2- **hemorrhagic fever:** -hemorrhagic manifestations, positive tourniquet test 3- **Dengue shock syndrome**: (Cold skin, rapid pulse)	**Clinical features:** **•low to moderate fever** **•bleeding and disseminated intravascular coagulation** •Abdominal pain •malaise •Encephalopathy or Encephalitis •nausea and vomiting •Diarrhea •Renal failure •Liver failure •muscle pain, back pain, and joint pain
Clinical features	(Diarrhea or constipation) 1st week: **fever, chills**, relative bradycardia 2nd week: **rose spots** 3rd week: **hepatosplenomegaly**	**•Undulant fever** **• Night sweats** **•Fatigue** •Anorexia •Weight loss •Arthralgia		
Diagnosis	1-**WBC: leukopenia** 2-**Culture**: **-Blood: most important at onset** -Bone marrow: most sensitive but invasive -stool culture: 2nd,3rd weeks	1-Culture: sensitivity -blood (15%-70%) -bone marrow(80%-90%) but invasive 2- **Serology**: Standard agglutination test (SAT) Very sensitive and specific	**-RT-PCR (best)** -Detection of viral antigen -Serology	**-PCR** -ELISA for IgM
Treatment and prevention	**•Ciprofloxacin (1st choice, empiric)** **•Ceftriaxone (2nd choice)** Prevention by: Food and water safety, vaccination, education	**1st line: doxycycline + streptomycin** (avoid if above 65 of age) 2nd line: doxycycline + rifampicin Prevention: avoid contact with animal fluids, pasteurization of milk, well cooked meat	**-Symptomatic treatment (use acetaminophen)** -Hydration - Avoid NSAIDs in children Prevention: elimination of mosquito's habitat, protection from bites	-**Symptomatic** treatment Prevention: Vaccine for veterinary
Complications	**•Pneumonia** **•Meningitis** **•Osteomyelitis** **•Small bowel perforation**	1-**Osteoarticular** diseases are the most common form of focal brucellosis (Sacroiliitis, spondylitis) 2-**Neurobrucellocis** 3-**Endocarditis (the main cause of death)**	**Dangerous signs in hemorrhagic fever:** **•Intense abdominal pain** **•persistent vomiting** **•restlessness** **•sudden change from fever to hypothermia**	

L40- Endemic infections in The middle east

<table>
<tr><th></th><th>Cutaneous leishmaniasis</th><th>Visceral leishmaniasis</th><th>MERS-Cov</th><th>COVID-19</th></tr>
<tr><td>Introduction/ Epidemiology</td><td colspan="2">-Protozoal disease caused by leishmania parasite
-Transmitted by sand fly (phlebotomus papatasi) bite
1-cutaneous 2-muco-cutaneous 3-visceral
-Promastigotes injected > become Amastigotes in macrophages > multiply and infect other cells</td><td>-Betacoronavirus
-Transmission most likely from camel to human, also human to human
-incubation period (5 days)</td><td rowspan="2">-incubation period within 14 days of exposure (mostly 4-5 days):
1. Viral response phase: high viral replication.
2. Pulmonary phase: decrease in viral replication and increase immune reaction.
3.Hyperinflammation phase: immune reaction is high and is associated with ARDs and shock.</td></tr>
<tr><td>Pathogenesis</td><td>-males more than females
-L.major, L.tropica
-concentrated in six regions: Al-Qaseem, Riyadh, Al-Hassa, Aseer, Ha’il, and Al-Madinah</td><td>-Kala Azar
- L.donovani, L.infantum, rattus rattus
-replicate in reticulo-endothelial system (hepatosplenomegaly)</td><td></td></tr>
<tr><td>Clinical features</td><td>-Pink papule leading to painless ulceration with indurated borders
-most common to the face</td><td>-asymptomatic or fever, malaise and weight loss
-splenomegaly
-Anemia , Leukopenia, Thrombocytopenia,
-Hyper-gammaglobulinemia
-Hypoalbuminemia, and edema.</td><td>1-Asymptomatic
2 -Fever (>38°C)
3 SOB
4 Cough
-CBC: lymphocytosis, pancytopenia..
-LFT: Elevated enzymes and LDH.
-RFT- Rising blood urea nitrogen and creatinine.)
-imaging: Ground-glass opacity, Airspace patchy infiltrates or consolidation.</td><td>●Mild case:
-fever, headache and dry cough
- loss of taste and smell
●Severe cases:
-respiratory failure
-cardiac (arrhythmia)
-neurologic (Encephalopathy)
-Thromboembolic (deep vein thrombosis and stroke)
●Risk factors for poor outcome:
-Increased age.
-Presence of chronic illnesses</td></tr>
<tr><td rowspan="2">Diagnosis</td><td>Aspiration From ulcer margins</td><td>Bone marrow/spleen aspiration</td><td rowspan="2">●RT-PCR
-Nasopharyngeal swab
Lower respiratory tract</td><td rowspan="2">●RT-PCR
-Nasopharyngeal swab, Lower respiratory tract (Optimal time 5-7 days post exposure)</td></tr>
<tr><td colspan="2">-Histopathology with Giemsa stain (Amastigotes)
- culture in Schneider's drosophila or NNN media
- PCR</td></tr>
<tr><td rowspan="2">Treatment and prevention</td><td>●Cryotherapy
●paromomycin,imidazole.
● (sodium antimony gluconate; Pentostam).
● sodium stibogluconate (SSG)</td><td>●Amphotericin B (even in pregnancy)
●paromomycin
●sodium stibogluconate (SSG)</td><td rowspan="2">●Supportive
Prevention: avoiding camels</td><td rowspan="2">●Supportive
●Low dose dexamethasone:</td></tr>
<tr><td colspan="2">Prevention: clothing, insect repellent, educate</td></tr>
</table>

L41-Osteoarthritis

◄ Definition

- Mechanical **wear and tear** destroys articular cartilage **(degenerative joint disorder)**

◄ Etiology

- **Heritable metabolic causes:** alkaptonuria, **hemochromatosis**, wilson disease
- **Hemoglobinopathies** : sickle cell disease, thalassemia
- **Neuropathic disorders leading to a Charcot joint**
- **Underlying morphological risk factors:** Congenital hip dislocation and slipped femoral capital
- **Disorders of bone:** Paget disease, avascular necrosis
- **Previous surgical procedures:** meniscectomy
- **Diabetes mellitus**

◄ Risk Factors

- **Age, obesity, trauma,** women gender, hypogondism (estrogen has protective role) muscle weakness, repetitive use, septic arthritis and crystal deposition

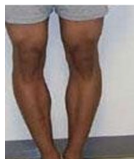
◄ Pathogenesis

- Degeneration of articular cartilage: is the defining feature of OA
- Consequent structural changes include **surface fibrillation** and **ulceration** with loss of cartilage that exposes underlying bone to increased stress, producing **microfractures** and **cysts** leading to abnormal **sclerotic subchondral bone** and overgrowths at the joint margins, called **osteophytes.**

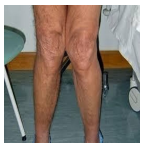
◄ Clinical Presentation

- **Pain**: Insidious onset, worse **with movement**, relieved by rest /**Brief (< 15 mins) morning stiffness**/ **Coarse crepitus** / **Asymmetric** joint involvement targeting the **hips, knees**, PIP, DIP, neck and lumbar spine/ Functional restriction/ No systemic symptoms

➔ Before labelling any pt to have OA you need to exclude inflammatory causes.



Genu Varum deformity
Primary OA ,The angle is **outward**



Genu Valgum deformity
indicates secondary OA (RA usually)

◄ Types of OA

- **Nodal OA:** Female preponderance. Pain, stiffness and swelling of **one or more PIP and DIP joints,** leaving painless bony swellings **Heberden's nodes (DIPs) and Bouchard's nodes (PIPs).** Involvement of the **first CMC joint** is also common causing **squaring of the thumb** base
- **Knee OA:** strong relationship with **obesity, bilateral with symmetrical** involvement, targets the patellofemoral and **medial tibiofemoral compartments** leads to a **varus "bow-legged" deformity**.
- **Hip OA:**
  - **Superior-pole hip OA :**
    - Most common, **unilateral**.
    - Affect the **upper surface of the femoral head** and adjacent acetabulum.
  - **Medial cartilage (central) loss:**
    - Usually affect women, **bilateral**.
    - Associated with hand involvement (NGOA). Has better prognosis.
- **Spine OA:** Cervical (cervical spondylosis) and lumbar spine (lumbar spondylosis) are the most common targeted sites. May be complicated with spinal stenosis or nerve root compression → neurological signs and radiation of pain.
- **Erosive OA:** an unusual group of patients with hand OA who have a more prolonged symptom phase and inflammation, more disability and worse outcome. Distinguishing features **subchondral erosions on X-rays,** occasional **ankylosis** of affected joints.

◄ Work up

- **X-ray:** Only abnormal when the damage is advanced.**narrowing joint space, Osteophytes, Subchondral sclerosis, and Cyst formation**
- **MRI of spine:** should be done **if nerve root compression or spinal stenosis are suspected.**
- **Bone scintigraphy:** to rule out malignancy
- **Arthrocentesis**: On suspicion of **septic arthritis. WBC : >100 OA, > 1000 Inflammatory**

L41-Osteoarthritis

◄ Treatment

Non pharmacological:

- Lifestyle modification: Physical and rehab therapy (OA of the knee you should exercise the quadriceps) , weight loss , medical shoes with lateral and medial wedged
- insoles.

Pharmacological:

- First choice: **Topical (NSAID)** due to less systemic side effects and it can be added at any step.
- **Topical capsaicin:** very irritating substance , pt should avoid touching the eyes after putting the cream, bc it may lead to conjunctivitis

If the topical therapy is failing, start oral therapy:

- First choice: **Acetaminophen**
- **Solpadeine**: Combination of acetaminophen and low dose codeine.

If all of above are failing even with combining oral and topical therapy go to the next step:

- Second choice: **NSAIDs (ibuprofen, meloxicam)**
- Third choice: **Tramadol** These aren't usually used can cause addiction, bc at this level (advanced OA) the only solution is arthroplasty
- **Duloxetine:** used in depression
- **Intra-articular corticosteroid injections** produce short-term improvement when there is a **painful joint effusion.**

L42- Gout

◄ Definition

- Gout is an inflammatory-arthritis **associated with hyperuricemia** and reaction to intra-articular monosodium urate crystals.
- Most commonly seen in elderly, men, and postmenuposal women due to the loss of estrogen induced uricosuric effect.

◄ Predisposing factors

- **Obesity & excessive weight gain.**
- **Increased intake** → Purine rich foods.
- **Diminished renal excretion** → Abnormal kidney function, alcohol intake, drugs (Thiazide & ASA, loop diuretics) Moderate to heavy alcohol intake (beer specially)
- **Generalised OA.**
- **Chemotherapy: Tumour lysis syndrome**
- **Increased production** → Inherited disorders: Lesch–Nyhan syndrome (X-linked recessive form of gout that is also associated with mental retardation) , High fructose intake

◄ Clinical Presentation

- **Acute monoarthritis:**
  - Sudden onset severe pain, extreme tenderness, and swelling of **the first MTP joint of the big toe.** Other common sites are the ankle, midfoot, knee, small joints of hands, wrist and elbow. The axial skeleton and large proximal joints are rarely involved.
  - Sudden onset, severe pain, extreme tenderness and marked swelling (giving impression of cellulitis).
  - Self limiting over 5-14 days.
  - Acute attacks may be precipitated by **dietary or alcoholic excess**, by **dehydration** or by **starting a diuretic.**
- **Chronic tophaceous gout:**
  - Chronic pain and joint damage.
  - Characterised with **Tophi**: irregular firm white nodules produced when crystals are deposited in the soft tissue on **extensor surfaces** of fingers, hands, forearm, elbows (difficult to differentiate from RA nodules), Achilles tendons and sometimes the helix of the ear.

L42- Gout

◄ Diagnosis

- Clinically or by rapid response to NSAIDs or colchicine.
- **Biochemical screen** → RFT, uric acid (can be normal or high), glucose and lipid profile, high ESR and CRP and neutrophelia.
- **Joint aspiration** (Synovial fluid analysis) → Cell count, polarized microscopy and culture to exclude septic arthritis and confirm the diagnosis.
  - Microscopy shows needle-shaped uric acid crystals (negatively birefringent).
- **X-ray** → normal in acute gout , well demarcated erosions in chronic gout.

◄ Management

- Patient presenting with acute monoarthritis: Give **antibiotics** and do not stop until the culture comes back negative.

- **Terminate acute attacks →**
  - **NSAIDS:** Fast onset of action, effective even after a few days of symptoms onset.
  - **Colchicine:** Slower onset, weak effect after 24-36 hours after symptoms onset, **narrow therapeutic index,** D/C if GI distress develops e.g. diarrhea or colicky abdominal pain.
  - **Corticosteroids:** for intolerant of NSAIDs or colchicine and Comorbidities.
  - **In renal impairment:**
    - Steroids are preferred, either intra-articular or systemic.
    - **Cr clearance < 50: Colchicine and NSAIDs are contraindicated.**
  - **Joint involvement:**
    - **Monoarthritis** → Intra-articular steroid injection is preferred, contraindicated in septic arthritis.
    - **Polyarthritis** → NSAIDs or Colchicine.

- **Prevent recurrence & reverse complications →**
  - **Use in :** tophi or radiographic changes or >2 attacks per year
  - **Xanthine oxidase inhibitors "decrease production":** Recommended urate levels <360 umol/L
    - **Allopurinol**: first choice, Start low, go slow, Dose adjust for renal function.
    - **Febuxostat**: more potent, there's a concern about **sudden cardiac death,** undergoes hepatic metabolism(CrCL > 30 mL/min - no dose adjustment)
  - **Uricosuric Agents "increase excretion":**
    - **Probenecid and Sulfinpyrazone:** have weaker action.
  - **Conjugated uricase enzyme:**
    - **Pegloticase:** treat **tophaceous gout resistant to standard therapy,** Used preventatively in people undergoing chemotherapy for **malignancies (tumour lysis syndrome).**

- **Address co-morbid conditions →**
  - Weight loss and decrease alcohol consumption.
  - Avoid if Possible organ meats e.g. liver, kidney and heart.
  - Limit Seafood sardines, tuna, mushrooms and high fructose corn syrup.
  - If possible, substitute the antihypertensive drugs that increase uric acid (e.g. thiazides, β-blockers and ACEI) with **losartan** which has uricosuric effect

L43: Use of Antibiotic

◄ Important considerations when prescribing antibiotics:

1. Obtain accurate diagnosis of infection

- Establishing a microbiological diagnosis, Especially for: **Endocarditis, Septic arthritis, and Meningitis**
- The most likely microbiological etiology can be inferred from the clinical presentation:
  - **Cellulitis** (streptococci or staphylococci) No need for positive culture → Empirical therapy
  - **Cellulitis with wound** and the patient has diabetic foot then probably it's **secondary cellulitis** from the wound itself, so organism will be the one in the wound not the usual ones.
  - Erysipelas (has demarcated margins unlike cellulitis, affecting the upper layers of the skin, while cellulitis affects the deeper tissues)
    - Erysipelas → Most common Strep
    - Cellulitis → Most common Staph
  - CA pneumonia with no risk factors can be treated empirically with **macrolide or cephalosporins antibiotic**
  - Community-onset UTI E.Coli: bactrim/fluoroquinolones or just nitrofurantoin if patient has cystitis only**.**
  - Identification of the infecting organism:
    - **Gram stain:** the simplest, least expensive, and most useful of all the rapid methods of identification of bacterial
      - Gram +ve cocci in clusters → staph. (coagulase -ve or coagulase +ve)
      - Gram +ve cocci in chains → enterococcus or streptococcus
      - Gram +ve diplococci → pneumococcal
      - Gram -ve diplococci → neisseria
      - Gram -ve rods → many
      - Gram -ve coccobacilli → brucella
    - **Direct detection of organisms:** Microscopy and Nucleic acid amplification (PCR)
    - **Tests of the host's specific immune response:** Antibody detection
    - **Culture of organisms:** shows the organism and its susceptibility, limitation results are not immediate, even for organisms that are easy to grow.

2. Empiric and definitive therapy

- **Susceptibility Testing:** the ability of a specific organism to grow in the presence of a particular drug; susceptible, resistant, and intermediate. Data are reported in the form of minimum inhibitory concentration
- **Timing of initiation of antimicrobial therapy:**
  - **Urgent cases:** Acute meningitis, Septic shock, Febrile neutropenia
    - Empiric therapy (broad-spectrum antimicrobial agents) should be initiated immediately after or concurrently with collection of diagnostic specimens.
  - **Non-Urgent cases:** hold antibiotics until appropriate specimens have been collected and submitted. Example**:**
    - subacute bacterial endocarditis → multiple sets of blood cultures
    - Wound infection, diabetic foot, chronic ulcers. Patient's discharging for 2-3 weeks and stable → debridement → then deep tissue culture
    - Febrile and stable patient with fever for several days with no clue to diagnosis.

3. Identify opportunities to switch to narrow-spectrum

- Every attempt should be made to narrow the antibiotic spectrum to reduce cost and toxicity and Prevent the emergence of resistance. **switch to oral agents as soon as possible.**

4. Cost-effective oral agents for the shortest duration necessary

- **Antimicrobial stewardship:** refers to the systems and processes applied to a population to optimise the use of antimicrobial agents. aims to improve patient outcomes and reduce antimicrobial resistance (AMR).
  - The appropriate **selection, route & duration, and dosing** of antimicrobials:
    - **The lowest effective dose** → avoid subtherapeutic doses
      - Serious vs non-serious infections
      - Drug PK/PD properties
      - Site of infection
      - Other host factors (e.g. renal function)

L43: Use of Antibiotic

◄ Important considerations when prescribing antibiotics cont':

4. Cost-effective oral agents for the shortest duration necessary

- **Antimicrobial Combinations: (Exhibits synergistic activity)**
  - **Rapid killing:** endocarditis caused by **enterococcus species** with a combination of **penicillin and gentamicin**.
  - **Shorten the course:** due to **viridans** group streptococci with a combination of **penicillin** or **ceftriaxone** with **gentamicin for 2 weeks.**
  - **Critical ill patient**
  - **Polymicrobial infections:** Intra-abdominal infections, diabetic foot such as third-generation cephalosporin or a fluoroquinolones **plus** metronidazole
  - **To prevent resistance:** combination of 4 anti-TB drugs in the first 2 months, then 2 anti-TB drugs for the rest of the course of treatment,

5. Understanding drug pharmacodynamics and efficacy at the site of infection.

Bactericidal	Bacteriostatic
Cause death by cell rupture and disruption of the bacterial cell. **Drugs act on:** 1) **The cell wall** (b-lactams most famous) eg. penicillins & cephalosporins & carbapenems & monobactams → they own b-lactam rings → antibiotic works on the cell wall production of bacteria. 2) **Cell membrane** (daptomycin) 3) **Bacterial DNA** (fluoroquinolones) - Preferred in the case of serious infections such as: - endocarditis - meningitis to achieve rapid cure	- Inhibit bacterial replication without killing the organism. Most common MOA - Act by inhibiting protein synthesis such as: 1) Sulfonamides 2) Tetracyclines 3) Macrolides

- **Oral** → for more stable patients providing that patient is tolerant to oral medications.
- IV → bacteremia, septic shock, infective endocarditis, severe meningitis.
- Candidates for treatment mild to moderate infections, well-absorbed oral antimicrobial agents :
  - **Pyelonephritis:** Fluoroquinolones
  - **Community-acquired pneumonia:** Augmentin and macrolides coverage
- The efficacy of antimicrobial agents depends on their capacity to achieve : Concentration equal to or greater than the MIC at the site of infection.
- **Ocular** fluid, **CSF**, abscess cavity, prostate, and bone are often much lower than serum levels
  - **First- and second-generation cephalosporins:** do not cross the blood-brain barrier. should **not** be used to treat them. eg. meningitis, endophthalmitis (similar to BBB)
  - **Aminoglycosides:** less active low-oxygen, low-pH, of Abscesses
  - **Fluoroquinolones** achieve high concentrations in the prostate preferred oral agents for the treatment of **Prostatitis**
    - **Moxifloxacin** does not achieve significant urinary concentrations therefore not suitable for treatment of UTIs because it is not excreted in the urine.
- Assessment of response to treatment: Clinical parameters, Laboratory values, Decreasing leukocyte count, Radiologic decrease in the size of an abscess.

6. Host characteristics that influence antimicrobial activity

- **Renal and Hepatic Function** (Adjust dose)
- **Pregnancy and Lactation**
  - **Sulphonamides**: A risk to develop **kernicterus** It can be used in the 2nd trimester. However, it's contraindicated in the 3rd trimester
  - **Tetracycline: Staining of the teeth**
  - **Fluoroquinolone: Cartilage damage**
  - **Thalidomide: Phocomelia**
- **History of Allergy or Intolerance: Penicillin and anaphylaxis**
- Genetic e.g, G6PD → avoid sulfa group in G6PD patients as it may lead to hemolysis
- Drug interactions

L43: Use of Antibiotic

Organism	Antibiotics
MRSA Methicillin Resistant Staph. Aureus (R mechanism: PBP2a penicillin binding protein)	• Vancomycin (Glycopeptide) • Teicoplanin (Glycopeptide) • Linezolid, Tedizolid • Daptomycin (Lipopeptide) • Telavancin (Glycopeptide) • Dalbavancin (Glycopeptide) • Oritavancin (Glycopeptide) • Ceftaroline (5th generation cephalosporins) • Tigecycline: cannot be used for pneumonia or bacteremia, only for intra-abdominal infections and skin and soft tissue infections • Delafloxacin: new fluoroquinolone agent • **Ceftobiprole** : 5th generation cephalosporins
VRE Vancomycin Resistant Enterococcus (common inside hospitals)	• Teicoplanin • Linezolid • Oritavancin • Tedizolid Daptomycin • Tigecycline and Eravacycline (new agents used only for intra-abdominal infections and skin and soft tissue infections, not UTIs since it isn't excreted in urine)
ESBL Extended Spectrum Beta-Lactamase ★	• **Carbapenems: drug of choice** • Piperacillin/tazobactam: increases mortality if given to severe infections. • Nitrofurantoin and fosfomycin (**UTI**): for very mild infections only. • Tigecycline and Eravacycline: for intra-abdominal infections and skin and soft tissue infections only • Colistin • Plazomicin • fluoroquinolones: like cipro and bactrim (depends on what you're treating)
CRE Carbapenem-Resistant Enterobacteriaceae Challenging infection, that carries high mortality and morbidity, need to produce new agents for treatment	• Nitrofurantoin and fosfomycin (UTI): for simple cystitis • Tigecycline and Eravacycline: for intra-abdominal infections and skin and soft tissue infections only. • **Colistin**: only one used for **NDM and OXA-45** → MOA of bacteria (covers BOTH MOAs) • Ceftazidime/avibactam and Meropenem/vaborbactam (new agents for OXA-45) • Plazomicin (used for OXA-45 only) Perform PCR to see what's the mechanism of resistance, based on this we choose the abx
Actinobacter Very bad, fast growing problem, especially in ICU pt and it has very limited choices of abx	• Carbapenems: 70% of actinobacter are carbapenem resistant, use if sensitive • Tigecycline and Eravacycline : for intra-abdominal infections and skin and soft tissue infections only (This organism mostly causes pneumonia in ICU, these two abx cannot be used for pneumonia) • Aminoglycosides, Colistin (only saving agent, but has many problems including dosing, they are nephrotoxic and not enough alone)
Pseudomonas aeruginosa Very famous hospital acquired infection ★	• Piperacillin/tazobactam: From all penicillins this is the only one that cover psuedomonas. ★ Ceftazidime (3rd) and cefepime (4th) and **Ceftobiprole** (5th generation cephalosporins) These are the only cephalosporins that cover pseudomonas • Meropenem, imipenem and Doripenem (carbapenem group) • Aztreonam • Some fluoroquinolones (only **ciprofloxacin** and levofloxacin) • Aminoglycosides • Colistin • Ceftolozane/tazobactam and Ceftazidime/avibactam (new agents).

L43: Use of Antibiotic

◄ Antimicrobial agents as prophylaxis:

- **Presurgical Antimicrobial Prophylaxis:** to reduce the incidence of postoperative surgical site infections.
  - A single dose of cephalosporin (such as cefazolin) administered within 1 hour before the initial incision is appropriate for most surgical procedures.
- **Prevent Transmission of Communicable Pathogens to Susceptible Contacts:**
  - Ciprofloxacin or Rifampicin for close contacts of a patient with N.meningitidis
- **Antimicrobial Prophylaxis Before Dental Procedures:** Prosthetic valves, Rheumatic heart, Unrepaired congenital heart disease, Previous infective endocarditis → to prevent endocarditis

◄ Positive culture in the absence of disease

- **Colonization occurs frequently in:** older women with indwelling urinary catheter, mechanically ventilated patients (endotracheal tubes), or chronic wounds.
- **No need to treat colonization** except in special cases (e.g. UTI +ve culture, if patient is pregnant or symptomatic or going for a procedure → treat)

◄ Antimicrobial decision making

When most culture results are available, one of the following five decisions should be made:

- **Stop antibiotic treatment**
- **Step down to an oral alternative**: For uncomplicated infections
- **Switch treatment**: because of an unanticipated site of infection (e.g. infective endocarditis requiring prolonged intravenous antibiotic treatment) or unanticipated resistance (such as urosepsis and bacteraemia caused by an **ESBL-producing E. coli requiring treatment with an intravenous carbapenem**).
- **Continue with intravenous treatment**: The patient has a more complicated infections
- **Discharge on outpatient parenteral antibiotic treatment**:

L44- Pitutary disorders

	Functional adenoma	Non-functional adenoma (incidentaloma)
Epidemiology	10 % of all pituitary lesions • Genetically-related to MEN-1, Gs-alpha mutation, PTTG gene, FGF receptor-4) • Or idiopathic	1.5 -31% in autopsy (prevalence) 10% by MRI most of them < 1 cm
Clinical (History and Examination)	• Function (oversecretion or hyposecretion) • Mass (headache,visual symptoms)	• **Asymptomatic** • Incidentaloma by imaging. • Mass-effect (Bitemporal hemianopia) • Gonadal hypersecretion
Biochemical	Screen Test, Confirmatory Test	**GH, LH, FSH, TSH, ACTH:** not high. **PRL could be:** low, high or normal.
Anatomy	**MRI** of sella turcica (MRI is superior to CT)	
Treatment	• Surgical >Medical >Radiation or Medical >Surgical >Radiation (Depend on the type)	• Surgery if indicated • Observation • Adjunctive therapy

1- Prolactinomas	
General info	• **Prolactinomas are the most common of functional pituitary adenomas**
Causes of hyperprolactinemia	• Prolactin secreting pituitary **adenoma** (Most common) • **Renal failure** (returns to normal after transplant), **Liver failure**, **primary hypothyroidism** (high TRH levels stimulate prolactin). • **Drugs** which interfere with dopamine: (Phenothiazines, Domapine receptor antagonists metoclopramide, a-methyldopa, verapamil, H2 blocker, estrogen, opiates, reserpine). • **Pregnancy** is the most common **physiological** cause.
Clinical features	• **Galactorrhoea**, oligo or amenorrhoea, infertility, Decreased libido, subfertility, erectile dysfunction, gynecomastia • It may have mass effect ⟶ Bitemporal hemianopia
Diagnosis	• **Serum prolactin level:** At least 3 measurements should be taken, Very high level suggests prolactinoma (>5000mU/L). • **Thyroid function test:** TSH must be tested to rule out primary Hypothyroidism. • **IGF-1** must be tested to rule out acromegaly co-secretion. • **Pregnancy test:** Always exclude pregnancy first
Treatment	***1st line:*** • **Medical:** Dopamine agonist drugs (e.g. Bromocriptine,Cabergoline (Drug of choice), Quinagolide) (Bromocriptine is preferred in pregnancy) **2nd line:** • Surgery and radiation

L44- Pituitary disorders *(cont.)*

2- GH excess (Acromegaly/Gigantism)	
General info	• **98% of cases are due to GH pituitary adenoma**

Clinical features	• **The most common complaints are headache and sweating.**
	• **Acral enlargement:** large thick hands & feet with osteoarthritis
	• **Gross features of acromegaly:** Face gross features, enlarged tongue, and jaw
	• **Galactorrhea** (Due to co-secretion of prolactin from the tumor)
	• Gingiva enlargement, constipation and **deep voice**
	• May have mass effect → Bitemporal hemianopia
	• Carpal tunnel syndrome (Median nerve compression)
	• **irreversible cardiovascular effect: (major cause of death)**
	  ○ **Cardiomegaly and CHF with Diastolic dysfunction being an early sign of cardiomyopathy.**
	  ○ **HTN** in 40%, LVH in 50% and they present with **Obstructive sleep apnea** (due to Neck enlargement)

Diagnosis	• **Initial test (screen): Measure IGF-1.** (Will be high in acromegaly) • **Confirmatory Test: 75g OGTT for GH suppression** • **MRI** or CT for the pituitary

Treatment	***1st line:***
	• **Surgery**
	2nd line:
	• **Medical:**
	  ○ **Somatostatin analogues (octreotide, lanreotide or pasireotide).**
	  ○ Dopamine agonist (**bromocriptine or cabergoline**) "especially **if associated with prolactin excess**"
	  ○ **Didn't work?** use GH receptor antagonist (Pegvisomant)
	3rd line:
	• **Radiotherapy**

3- Diabetes insipidus	
Types	• **Central DI:** Deficiency of vasopressin (ADH), caused by a hypothalamic disorder (adenoma of pituitary does not cause it because it is only stored there) • **Nephrogenic DI:** Renal resistance to ADH action • **Psychogenic DI:** is an excessive water intake seen in some patients with mental illnesses such as schizophrenia.
Symptoms	• Abrupt onset of **polyuria** (1st manifestation), **polydipsia** (2nd manifestation)
Investigations	• **Urine: ↑urine volume** (2 – 15 L/day), **↓urine osmolality,** ↓specific gravity . • **Serum Na+:** usually **high** • High or high-normal plasma osmolality **Water deprivation test** (To differentiate between CDI,NDI and PDI) • **Central DI:** urine osmolality will still low (Before giving vasopressin) and returns to normal after administer vasopressin. • **Nephrogenic DI:** exogenous vasopressin does not alter urine osmolality much. • **Psychogenic DI:** Urine will be become concentrated as they aren't really a problem with either the pituitary nor the kidney
Treatment	CDI → DDAVP. NDI→ Correct underlying cause, Hydrochlorothiazide.

When The Level of Glucose is high:

- **Hormone**: **Insulin**
- ↑ glycolysis
- ↑ ion uptake especially K and PO_4^{3-}
- ↓Ketogenesis
- Effect on **Liver**:
1. ↑ Glycogen synthesis

- Effect on **Liver**:
1. ↑ Glycogen synthesis
2. ↓ Gluconeogenesis
3. ↓ Glycogenolysis
4. ↑ lipogenesis (FA synthesis)
5. ↑ Lipoprotein synthesis

- Effect on **Muscles**:
1. ↑ protein synthesis
2. ↓ Proteolysis
- Effect on **Adipose tissue**:
1. Inhibition of intracellular lipase > No lipolysis
2. ↑ TGs deposition

	T1DM	T2DM
pathogenesis	- Interactions of genetic, environmental, and immunological factors that lead to the destruction of the pancreatic Beta cells and insulin deficiency. - Most, but not all, individuals have evidence of islet-directed autoimmunity. - There is a loss of both first and second phase of insulin secretion.	Two defects are necessary: - Abnormalities of insulin action:(resistance), characterized by ability of insulin to: - Inhibit hepatic glucose output - Suppress lipolysis in adipose tissue. - Stimulate glucose uptake into skeletal muscle - Abnormalities of insulin secretion: - The body responses to insulin resistance by increasing insulin secretion, early sign is loss of the first phase of the normal biphasic insulin secretion. - This level is still inadequate to restore glucose homeostasis. By the time of diagnosis, at least 50% of B-cell mass and function has been lost. - Glucotoxicity thought to cause further B-cell loss and further deterioration of glucose homeostasis. With time, insulin secretion declines. 'Starling curve' of the pancreas.
Age	Usually <30y/o	Usually >30y/o
Course	Rapid From DPT-I can be indolent	Indolent Virtually none found on screening
risk factors	1- Genetic: HLA- DR3-DQ2, HLA- DR4-DQ8 or both. By contrast, certain HLA alleles confer protective effects, for example DQB1*0602. Increased susceptibility to type 1 diabetes is inherited but **the disease is not genetically predetermined.** 2- Environmental: - maternal factors: such as gestational infection and older age. - viral infection: such as Coxsackie B4. - Childhood obesity and early introduction of cow's milk.	- Diet: dietary fat, red and processed meat, consumption of fried food. - Aging: B-cell function declines with age - Obesity: accounts for 80-85% of the overall risk - Fetal origins of diabetes: low weight at birth associated with glucose intolerance later in life - Physical inactivity. - Genetic susceptibility and inheritance: Identical twins have more than a 50% chance - TNF-alpha may induce insulin resistance in obesity - Others: urbanization, poverty, abnormal sleep patterns, environmental toxins and mental illness.

Bolus (preprandial or mealtime) insulins	Basal insulin
Rapid-acting insulin analogues (clear) - Insulin aspart (NovoRapid®) - Insulin lispro (Humalog®) - Insulin glulisine (Apidra®) - Faster-acting insulin aspart (Fiasp®)	Intermediate-acting (cloudy) - Insulin neutral protamine Hagedorn (Humulin® -N, Novolin® ge NPH)
Short-acting insulins (clear) - Insulin regular [Humulin®-R, Novolin® ge Toronto] - Insulin regular (Entuzity®)	Long-acting insulin (clear) - Insulin detemir (Levemir®) -Insulin glargine U-100 (Lantus®) - Insulin glargine U-300 (Toujeo®) - Degludec U-100, U-200 (Tresiba®) - Insulin glargine biosimilar (Basaglar ®)
Premixed insulins	
Premixed regular insulin –NPH (cloudy) - Humulin 30/70 - Novolin® ge 30/70, 40/60, 50/50	Premixed insulin analogues (cloudy) - Biphasic insulin aspart (NovoMix® 30) - Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)
insulin complications	
- Hypoglycaemia (The most common) ,Weight gain, Insulin antibodies, insulin resistance, Peripheral oedema, Local allergy (rare), Lipohypertrophy or lipoatrophy at injection sites	

Biguanides: metformin

increases insulin sensitivity, peripheral glucose utilization and reduces gluconeogenesis
first-line pharmacological agent in all type diabetes guidelines.

GI: anorexia, nausea, abdominal discomfort and diarrhoea.

- Contraindicated in: renal impairment, cardiac failure and hepatic failure because of the risk of lactic acidosis.

Sulphonylureas

Gliclazide, Glimepiride, Glibenclamide, Glipizide, Tolbutamide

Act on the B cell to induce insulin secretion. no effect in people with type 1 diabetes.
can be used as an alternative first-line agent where metformin is contraindicated or not tolerated.

Adverse effects:Weight gain and hypoglycaemia.

- used with care in people with liver or renal disease.

Thiazolidinediones : pioglitazone

Reduce insulin resistance by interaction with peroxisome proliferator-activated receptor-gamma (PPAR-Y), a nuclear receptor that regulates large numbers of genes, including those involved in lipid metabolism and insulin action.

Pioglitazone may specifically benefit people with non-alcoholic fatty liver disease, a frequent co-morbidity of type 2 diabetes.

Adverse effects: weight gain, fluid retention.

Meglitinides or post-prandial insulin releasers

Repaglinide, Nateglinide

Mode of action Like sulphonylureas, meglitinides act by closing the K*-ATP channel in the ß cells have a short duration of action of less than 3 hours.
used to treat people with post-prandial hyperglycaemia with normal fasting glucose levels.
Hypoglycaemia and weight gain but these are generally less severe than with sulphonylureas.

Dipeptidyl peptidase-4 inhibitors or 'gliptins

Sitagliptin, Linagliptin, Vlidagliptin, Alogliptin, Saxagliptin

These drugs inhibit the enzyme DPP4, which prevents the rapid inactivation of glucagon-like peptide-1 (GLP-1), which increases insulin secretion and reduces glucagon secretion.
most effective in the early stages of type 2 diabetes, when insulin secretion is relatively preserved, and are currently recommended for second-line use in combination with metformin or a sulphonylurea.
Occasional reports of acute pancreatitis., Saxagliptin may increase the risk of heart failure.

GLP-1 receptor agonist

Exenatide, Liraglutide, Lixisenatide, Dulaglutide, Semaglutide, Albiglutid

more potent that DPP-4 inhibitors. they also act on the hypothalamus to reduce appetite and food intake leading to weight loss. The size of effect has led to the licensing of liraglutide as an anti-obesity treatment.
now used in combination with other antidiabetic agents, as second- or third-line therapies. They should not be combined with DPP-4 inhibitors
Adverse effects: gastrointestinal and include nausea and vomiting, bloating and diarrhoea.

Sodium-glucose transporter 2 inhibitors ('flozins')

Dapaglilozin ,Empaglilozin, Canaglilozin

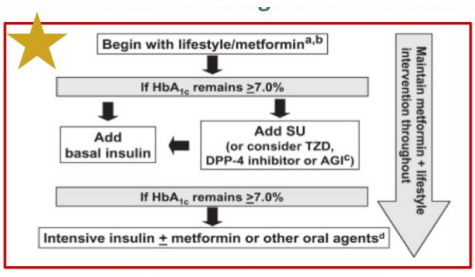
In addition to their effects on blood glucose, they lower body weight, improve renal dysfunction and reduce the risk of atherosclerotic cardiovascular events and heart failure

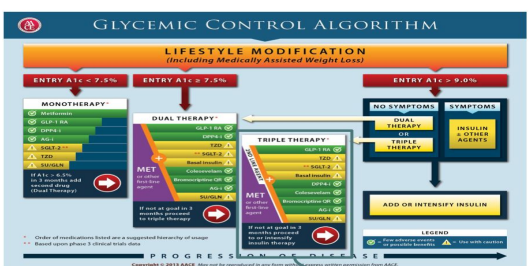
- Lower the renal threshold for glucose, increasing urinary glucose excretion.
- can be used as monotherapy but are used more typically in combination with all other antidiabetes drugs.
- This class has become rapidly established in clinical practice and in type 2 diabetes guidelines because of their cardiovascular benefits, weight loss and low risk of hypoglycaemia. SGLT2 inhibitors are licensed as adjunctive therapy to insulin in type 1 diabetes.
- Adverse effects : genital candidiasis and dehydration.
- Rarer side effects include diabetic ketoacidosis, Fournier's gangrene and lower limb amputation.

Alpha-glucosidase inhibitors

Acarbose ,Miglitol ,Voglibose

Can be used as monotherapy or in combination with all other antidiabetes drugs, they are not widely used because of their limited efficacy and gastrointestinal side-effects.
The major side-effects are gastrointestinal and include flatulence, abdominal distension and diarrhoea, as unabsorbed carbohydrate is fermented in the bowel.





L47-Diabetic Complications

◄ How to Reduce the Risk of Diabetes Complications?

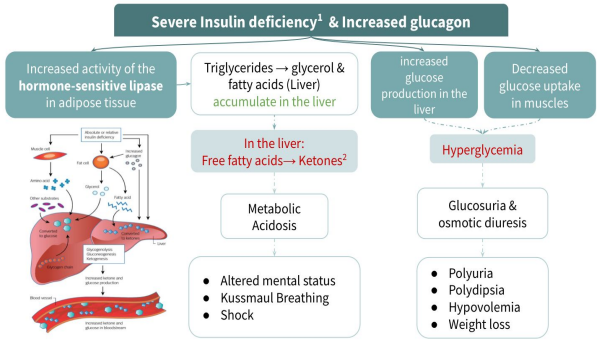
- Maintain a good glucose control (A1C around 7%)

◄ Diabetic Ketoacidosis (DKA)

- Status of metabolic acidosis due to absolute (or relative) insulin deficiency in association with increased levels of glucagon and other counter-regulatory hormones resulting in increased ketone production.

- **Precipitating Causes of DKA**
  - Non compliance with insulin therapy
  - Drugs: SGLT-2 inhibitors
- **Clinical Features of DKA**

◄ Pathophysiology of DKA



*The most important biochemical abnormality in is the uncontrolled lipolysis due to increased activity of hormone-sensitive lipase in adipose tissue and uncontrolled ketogenesis in the liver.

-Polyuria, Polydipsia, Weight loss, abdominal pain,Hypothermia, change in mental status, Nausea and Vomiting, Deep labored breathing (Kussmaul respiration), Dehydration (as a consequence of two parallel processes):

- Hyperglycemia
- Renal hypoperfusion

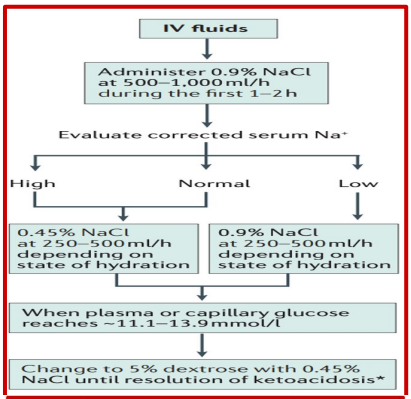
- **Laboratory Findings in DKA**
  - Hyperglycemia >250 mg/dL + Hyperketonemia (or heavy ketonuria) +High anion gap (> 12 mmol\l) metabolic acidosis <18 mEq/L
  - Blood electrolytes should be assessed as potassium abnormalities occur frequently
- **Management of DKA**
  - Aggressive rehydration + Lowering glucose + Cessation of ketogenesis + Correcting electrolyte imbalance

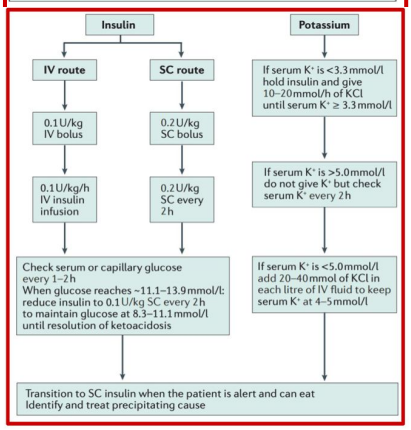
1) Rehydration

- IVF is the most critical step.
- Once the plasma glucose is ~250 mg/dl, switch IVF to D5% IVF.

2) Insulin

- Insulin is the next step after IVF
- Reduces serum glucose, suppresses ketogenesis, and correct the electrolyte disturbance.
- Most of the time: we use IV insulin infusion
-





3) Electrolytes

- DKA is associated with total-body K+ deficit
- Serum K+ is often normal or high (do not get fooled!) .
- K+ Shift from intracellular to extracellular compartment with acidosis (serum K+ looks falsely normal). Metabolic acidosis causes hyperkalemia as potassium is exchanged for hydrogen ions moving into the cell. As insulin promotes the co-transport of potassium along with glucose into cells. Although serum potassium may be elevated, there is a severe whole-body potassium deficiency as significant quantities of potassium are lost in vomit and urine.
- Insulin therapy moves K+ back into the cells (watch for a drop in K+).

4) Restoration of the acid-base balance

- Consider bicarbonate infusion if pH <7

◄ Hyperglycemic Hyperosmolar State (HHS)

- Status of severe hyperglycemia due to **insulin resistance** (not absolute insulin deficiency) & relative insulin deficiency resulting in increased serum osmolality.
- What is the characteristic metabolic emergency of uncontrolled type 2 diabetes?
- Severe hyperglycemia development without significant ketosis
- **Lab findings**
  - Severe hyperglycemia (> 30 mmol/L (600 mg/dL)
  - Hyperosmolality (serum osmolality >320 mOsmol/kg)
  - Without significant ketonaemia (<3 mmol/L) or acidosis (pH >7.3 (H+ <50 nmol/L), bicarbonate >15 mmol/L)

Management of HHS

- Management of HHS is similar to that of DKA
- The most important aspect of management is fluid replacement; 0.9% sodium chloride is the treatment of choice

but 0.45% sodium chloride may be considered if the osmolality is not declining despite adequate fluid balance.

◄ Hyperglycemic Hyperosmolar State (HHS)

- Plasma glucose <3.9 mmol/L (<70 mg/dl)
- Severe hypoglycemia: need for assistance from another person to correct glucose
- What is the most frequent & serious adverse effect of glucose-lowering therapies such as insulin? Hypoglycemia
- **Clinical features:**
  - related to acute activation of the autonomic nervous system
  - secondary to glucose deprivation of the brain (neuroglycopenia)
- **Management of Hypoglycemia:**
  - Give 15 grams of carbohydrates
  - Wait 15 minutes and re-check glucose
  - Repeat the same if glucose is still less than 70 mg/dl
  - If glucose is above 70 mg/dl, have the patient eat a regular meal or a snack that contains protein

◄ Diabetic retinopathy

- **Most commonly diagnosed diabetes-related complication**

1) **Non-proliferative (earliest change):** Usually appears in the 1st decade of the disease or early 2nd decade, Characterized by retinal vascular microaneurysms, blot hemorrhage, and cotton-wool spots
2) **proliferative:** Hypoxemia & neovascularization leading to virtuous hemorrhage, fibrosis, and retinal detachment
3) **Macular edema**
   can occur in non proliferative or proliferative stage

- **Treatment :**
  - Prevention (most effective treatment) ⟶ easier than treating

◄ Diabetic Nephropathy

- If your patient with diabetes has nephropathy but no retinopathy; it is very likely that the nephropathy is NOT due to diabetes
- Screen with Urinary Albumin: Creatinine & eGFR
- Albuminuria (Albumin: Cr >30 mg/g)
- Prevention (most effective treatment)
  - ACEI (or ARBs) are recommended to treat nephropathy.
  - SGLT-2 inhibitors can be used, decrease the risk and progression of diabetic nephropathy.

◄ Diabetic Neuropahty

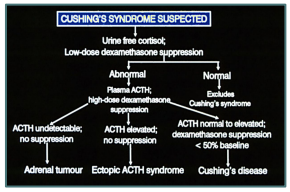
- Treat with preventive foot care
- What is the most common form? distal symmetric polyneuropathy

L48- Adrenal Disorders

<table>
<tr><th colspan="4">Primary adrenocortical insufficiency (Addison's disease)</th></tr>
<tr><td>Causes</td><td colspan="3">Major:
• Autoimmune (The most common cause)
○ Type I (APECED) : affects children: Adrenal insufficiency, hypoparathyroidism, pernicious anaemia, chronic candidiasis, chronic active hepatitis, and hair loss)
○ Type II (Schmidt's syndrome) usually affects young adults : hypothyroidism, adrenal insufficiency and diabetes mellitus, vitiligo
• Tuberculosis
other:
• Infection, Infiltration, Iatrogenic, Medications, Hereditary, Miscellaneous.</td></tr>
<tr><td rowspan="2">Evaluation</td><td>Clinical</td><td>Biochemical</td><td>Anatomical</td></tr>
<tr><td>Hyperpigmentation, weakness and fatigue, weight loss, anorexia, and GI disturbances, hypoglycemia, salt craving, amenorrhea, hypotension (Think about Adrenal insufficiency if not respond to IVF and initial management)</td><td>- Hyponatremia, hyperkalemia. mild to moderate hypercalcemia
- Measure a.m. cortisol:
• If high: rule out
• If very low : diagnosis
• If borderline result : proceed for confirmatory test (ACTH stimulation test)
- Measure ACTH Plasma levels:
it differentiates between primary and secondary</td><td>Adrenal insufficiency is clinical and biochemical diagnosis , no indications to do imaging unless clinically indicated such as:
• Patient on anticoagulation
• Malignancy with metastasis
• Other infiltrative disease</td></tr>
<tr><td>Treatment</td><td>• IVF: dextrose and salt
• Electrolytes replacement</td><td>Steroid replacement for primary adrenocortical insufficiency:
• hydrocortisone
• Fludrocortisone</td><td>Steroid replacement for secondary adrenocortical insufficiency:
• hydrocortisone only</td></tr>
<tr><th colspan="4">Secondary/ Tertiary adrenal insufficiency</th></tr>
<tr><td>Causes</td><td colspan="3">• The commonest cause of ACTH deficiency is exogenous glucocorticoid administration.
• Pituitary/hypothalamic tumors are the most common causes of naturally ACTH hyposecretion.</td></tr>
<tr><td>Clinical Features</td><td colspan="3">• The clinical features may be non-specific, Hypoglycemia is occasionally the presenting feature.
• hyperpigmentation and Electrolytes abnormalities are absent.</td></tr>
<tr><th colspan="4">Congenital Adrenal Hyperplasia</th></tr>
<tr><td>Clinical Features</td><td colspan="2">• 90–95% of CAH cases are caused by deficiency of 21-hydroxylase enzyme.
• Ambiguous genitalia (Female)
• Failure to thrive
• Dehydration & Shock (usually male)</td><td>• Salt-loss presentations with electrolytes imbalance:
○ Hyponatremia
○ Hyperkalemia
○ Hypoglycemia
• Hyperpigmentation</td></tr>
<tr><td>Diagnosis</td><td colspan="3">Clinical:
• History and examination (B.P)
Biochemical:
• Low Na & high K, fasting hypoglycemia, elevated serum urea, elevated plasma Renin & ACTH levels, low Cortisol, High 17 – OHP, High androgens especially testosterone level, Low Aldosterone (in salt losing types only).</td></tr>
<tr><td>Treatment</td><td colspan="3">Hydrocortisone, Fludrocortisone, During adrenal crisis (intravenous hydrocortisone), IVF D5 0.9% saline, In vomiting or diarrhea (parental therapy is indicated), Medical Alert: bracelet.</td></tr>
</table>

L48- Adrenal Disorders

Hypercortisolism (Cushing Syndrome)

	Clinical	Biochemical	Anatomical
Approach	**- Rounded "moon" facies** with a plethoric appearance, **truncal obesity** with prominent supraclavicular and dorsal cervical fat pads **"buffalo hump"**, distal extremities and fingers are slender, muscle wasting and weakness, the skin is thin and atrophic, with poor wound healing and **easy bruising, purple striae** may appear on the abdomen, **hypertension,** renal calculi and osteoporosis. - **Hyperpigmentation** is common in the ectopic ACTH.	• High cortisol • High ACTH (ACTH dependent) and low if (non-ACTH dependent). • 24hrs for UFC • 1MG DST • Midnight salivary cortisol 	**If ACTH:** • **high: MRI pituitary** • **low: history then CT adrenals** Small tumors may be difficult to detect and selective venous sampling may be needed. In some cases, more detailed isotope scanning and **arteriography or venography may be needed.**
Treatment	**- Adrenal tumors**: **adenomas** are successfully treated by **adrenalectomy,** when adrenal cancer cannot be fully resected or there is metastatic disease that can't be identified, give mitotane. **- Ectopic ACTH syndrome:** therapy is directed at **removal of the tumour.** **- Cushing's disease:** Trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice.		

Conn's Syndrome

Causes	• Primary hyperaldosteronism: Adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex, rarely adrenal carcinoma, Bilateral adrenal hyperplasia; idiopathic AH, Indeterminate hyperaldosteronism, Dexamethasone suppressible hyperaldosteronism.	
Clinical and Lab. findings	• Secondary HTN, High Na, high Cl, high Aldosterone, Alkalosis and low K (episodic weakness, Paresthesias, transient paralysis, tetany, nephropathy with polyuria and polydipsia)	

Biochemical Investigation	**Screening test:**
	• aldosterone/renin ratio
	  ○ If high: do confirmatory test
	  ○ If low: look for secondary causes
		Confirmatory test:
		• Saline infusion test
		• Oral salt loading test
		• Captopril test
		• Fludrocortisone suppression test

Treatment	Adenoma ⟶ Surgical resection	Adrenal hyperplasia ⟶ Spironolactone

Pheochromocytoma

Clinical Features	50% are silent. (NO symptoms), Isolated or part of MEN type II A or MEN type II B, Episodic (spells): sweating, palpitation, headache, Typical symptoms are **(Secondary HTN,** Young age < 40, 3 anti-HTN medications, Resistant HTN and Accelerated HTN.

Investigation	• **Biochemical:** The best initial test is the level of free **metanephrines in plasma**, 24 hr urine collection of Metanephrines(2X) (Confirmatory Test).
	• **Anatomical:**
	  ○ CT scan = MRI
	  ○ MIBG if: Paraganglioma, Young, Large size, malignant features
	  ○ Genetic Tests

Management	**before the surgery we need to:** • **Control HTN**: α-blocker2 then B-Blocker, Ca-blockers: can be used • **Salt loading:** Oral NaCl for 3 days Or IVF 0.9% saline 1-2 days before surgery • **Surgical removal:** Surgical tumor resection with early ligation of venous drainage is the treatment of choice.

L49- Parathyroid disorders

Hyperparathyroidism

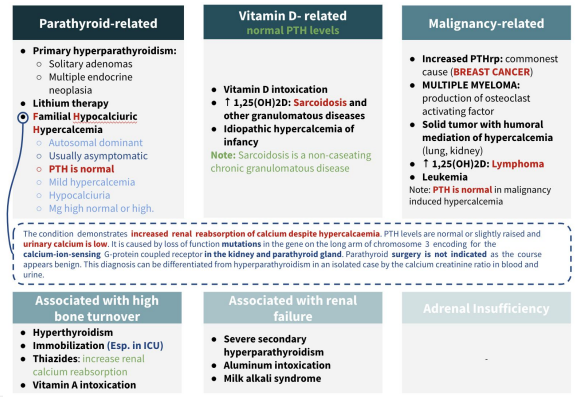
General info

- Excessive production of PTH
- A single adenoma occurs in about 80% of patients with primary hyperparathyroidism.
- Four glands hyperplasia account for 15-20% of cases.

Clinical features

- Classic presentation: Stones, Bones, Abdominal groans and Psychic moans
- The most common presentation: Asymptomatic hypercalcemia
- Osteitis fibrosa cystica (In advanced disease) is a cystic bone spaces filled with brown fibrous tissue (“ brown tumor” consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain).

DDX of hypercalcemia



Diagnosis

- **Lab:** ↑ Calcium, ↓ Phosphorus, ↑ PTH; when this combination is present in an asymptomatic patient then further investigation is usually unnecessary.
- **24-hour urinary calcium or single calcium creatinine ratio** should be measured in a young patient with modest elevation in calcium and PTH to exclude familial hypocalciuric hypercalcaemia
- **Plain X-ray of hands** can be diagnostic showing **subperiosteal bone resorption** usually on the **radial surface of the distal phalanx with distal phalangeal tufting** as well as **cysts** formation and generalized osteopenia
- Preoperative localization of the abnormal parathyroid gland(s): **Thallium 201 – Tehcnichum99m scan (subtraction study) and sestamibi scan** (85-95% sensitivity)

Treatment

- If patient is symptomatic (lithiasis, osteoporosis, pancreatitis) surgery (Parathyroidectomy) is indicated.
- **During surgery the surgeon identifies all four parathyroid glands (using biopsy if necessary) followed by:**
  - The **removal of the enlarged parathyroid, not all the 4 glands** (In case of **adenoma**)
  - Or **3 1/2 glands** in case of multiple glandular **hyperplasia**. (You can easily live with half a parathyroid gland)
- **Medical treatment:** cinacalcet (Calcimimetic agent) can be used if patient has high surgical risk e.g. elderly and dialysis patients

Secondary hyperparathyroidism

- Physiological compensatory hypertrophy of all parathyroids because of chronic hypocalcaemia.
- Causes: chronic kidney disease (Most common),

Tertiary hyperparathyroidism

- The development of apparently autonomous parathyroid hyperplasia after long-standing secondary hyperparathyroidism, most often in renal failure.

Hypoparathyroidism

General info	• **Deficient secretion of PTH** which manifests itself biochemically by **hypocalcaemia**, **hyperphosphatemia diminished or absent circulating iPTH** and clinically the symptoms of **neuromuscular <u>hyperactivity</u>**.
Causes	• **The most common causes are autoimmune or post-surgery** (Thyroidectomy) **Other causes:** • **Chronic hypomagnesaemia** • **"Polyglandular autoimmune syndrome Type 1 (AKA "Hypoparathyroidism – Addison's disease – mucocutaneous candidiasis (HAM) syndrome")":** In children (2-4y/o) and In this sequence (moniliasis "mucocutaneous candidiasis" → hypoparathyroidism →hypoadrenalism)

Clinical features	• The rate of decrease in serum calcium is the major determinant for the development of neuromuscular complications.
	• **Paresthesia and numbness around mouth, hands and feet and laryngeal stridor**
	• **Tetany (if severe acute hypocalcemia, usually post-surgical)**
	• Hyperventilation and carpopedal spasm
	• **Prolonged QT interval** in the ECG
	• **Posterio-lenticular cataract** in long standing hypocalcemia due to deposition of calcium phosphate.
	• **Signs of latent tetany :**
	  ○ **Chevostek sign:** Contraction of facial muscles on tapping on zygomatic arch
	  ○ **Trousseau sign:** Carpopedal spasm when inflating sphygmomanometer 20 mmHg above systolic BP
	  ○ Extrapyramidal signs (due to basal ganglia calcification): Parkinsonism usually occur in old individuals, if a young pt presented with Parkinsonism suspect hypocalcemia

Diagnosis	• In the **absence of renal failure** the **presence of hypocalcaemia with hyperphosphatemia** is virtually diagnostic of hypoparathyroidism. • **Undetectable serum iPTH confirms the diagnosis** or it can be detectable if the assay is very sensitive.
Treatment	**Acute and severe <u>with tetany</u> (emergency):** • Give 10 cc of 10% **calcium gluconate parenterally** slowly and under ECG monitoring (careful in patients on digoxin) **Chronic hypocalcemia:** • The mainstay of treatment is a combination of oral **calcium (1-2gm daily)** with pharmacological doses of **vitamin D (Calcitriol or alfacalcidol)** or its potent analogues. • Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level. always give active vitamin D because low PTH leads to decreased conversion of vitamin D to its active form at the kidney level.

Osteoporosis

- A common metabolic bone disease characterized by low bone mass. It most often affects thin postmenopausal women with risk doubling after 65 years of age. Men are also at risk for osteoporosis, but the diagnosis is often overlooked. Commonly asymptomatic until fractures occur.
- Exam may reveal hip fractures, vertebral compression fractures (loss of height and progressive thoracic kyphosis), and/or distal radius fractures (Colles fracture) following minimal trauma
- **Diagnostic test: DEXA** (Osteoporosis: Bone mineral density (T-score) is 2.5 standard deviations (SDs) less than normal. Osteopenia: T-score between 1 and 2.5 SDs below normal.)
- **Lifestyle modifications:** Adequate calcium and vitamin D intake (supplementation can be used for prevention), smoking cessation, avoiding heavy alcohol use, and weight-bearing exercises.
- **Best initial treatment: Bisphosphonates** (eg, alendronate, risedronate, ibandronate, zoledronic acid) are used in the treatment of osteoporosis, not osteopenia.

L50 - Dyslipidemia

◄ Lipoproteins

- **Particles that transport** transport the digestion products of dietary fat to the liver and peripheral tissues.
- **Types:**

	Chylomicrons	VLDL	IDL	LDL	HDL
Source	intestine	Liver	VLDL remnant	VLDL & IDL	intestine, liver
Atherogenicity	Not atherogenic (doesn't cause MI) but causes **pancreatitis**	+	+	+++	**Anti-atherogenic**

- **HDL** cholesterol is able to go and **remove cholesterol from the atheroma.**
- **Which one has the most atherogenic effect? Small dense LDL.**
- **Pathways:**

Pathway	Lipoprotein	Function	Enzyme
Exogenous (post-prandial)	Chylomicrons	Transport fats from the intestine to the liver	**Intestinal lipoprotein lipase**
Endogenous	VLDL → IDL	VLDL released to blood stream to form IDL	**Endothelial lipoprotein lipase**
Endogenous	IDL → LDL	Hepatic lipase breakdown IDL to form LDL → LDL carries fat & cholesterol to the cells	**Hepatic lipase**
Reverse cholesterol transport	HDL	**Nascent HDL*** carry fat and cholesterol from blood vessels (Periphery) to the liver.	

*** if you want to inject HDL, you inject nascent HDL because it is empty of cholesterol.**

◄ Hereditary causes of hyperlipidemia

- **Familial (Primary) hypercholesterolemia:**
  - **Dominant mutation in LDL receptor,** resulting in elevated levels of LDL at birth and throughout life.
  - **Heterozygous → Premature CAD (ages 30-50),** high risk for atherosclerosis, tendon xanthomas**,** tuberous xanthomas, xanthelasmas of eyes and arcus senilis (In younger ppl, it's called arcus juvenilis).
  - **Homozygous → CAD (before age 18),** total absences of LDL receptors.

- **Familial Combined Hyperlipidemia:**
  - Autosomal dominant.
  - **Raised cholesterol AND triglyceride** concentrations in association with a typical family history.
  - Increased secretions of VLDLs
  - **Fibrates** are the treatment of choice since these reduce both cholesterol and triglyceride concentrations.

- **Dysbetalipoproteinemia:**
  - Recessive.
  - Binding-defective form of apoE (which usually plays important role in metabolism of chylomicron and VLDL → High VLDL and chylomicrons).

◄ Primary hypertriglyceridemia

- **LPL deficiency** → hepatosplenomegaly, abd. cramps and **pancreatitis** at young age.
- **Apo C-II deficiency** → abd. cramps and pancreatitis.
- **Familial hypertriglyceridemia** → unknown enhanced hepatic TG-production, abd. cramps, pancreatitis and retinal vein thrombosis.

L50 - Dyslipidemia

◀ Secondary Hyperlipidemia

- **Secondary hypercholesterolemia (↑↑LDL)**
  - **Hypothyroidism**
  - **Anorexia nervosa**
  - **Pregnancy**
  - **Biliary obstruction PBC**
- **Secondary hypertriglyceridemia (↑↑VLDL)**
  - **Diabetes mellitus**
  - **Obesity**
  - **Uremia, dialysis**
  - **Alcohol** → **↑↑Chylomicrons**

◀ When to check lipid panel?

Different Recommendations:

- **Adult Treatment Panel (ATP III)** → Beginning at age 20, every 5 years.
- **US preventive services task force**→
  - **Women ≥ 45 years, Men ≥ 35** → **Total** and **HDL** cholesterol every 5 years.
  - If total cholesterol > 200 or HDL<40 → a fasting panel should be obtained.
  - **Cholesterol screening** → **Begin at 20 years in patients with a Hx of** → Multiple cardiovascular risk factors, DM, Family Hx of (Elevated cholesterol levels & Premature cardiovascular disease).

◀ Treatment

Goal of treatment:

- **Non-LDL** → To **prevent coronary heart disease outcomes** (MI & coronary death).
- **Triglyceride** → To prevent **pancreatitis** and may be CHD outcomes.

Non-medical treatment:

- **Lifestyle modification, Low-cholesterol diet, Exercise, Alcohol and Smoking cessation.**

Medication:

- **Statins** →
  - **HMG CoA reductase inhibitors.**
  - **Low intensity** → lowers LDL by <30%, **Medium intensity** → lowers LDL by 30 - 50%, **high intensity** → lowers LDL by >50%.

Stepwise approach:

1. Life style modification.
2. Does this patient have established coronary artery disease? (Had MI...)
   ✓ **If yes?** High intensity statin! except if pt is old >75.
3. Is his LDL more than 190?
   ✓ **If yes?** High intensity statin! No need for further questions
4. Has DM? More than 40 years?
   ✓ **If yes?** High intensity statin!
5. Anything other than that (2,3,4), we apply the 10 year risk assessment (done by websites & applications):
   - **If its less than 5%** → No need for meds
   - **Between 5%-7.5%** → needs moderate intensity statin.
   - **More than 7.5%** > needs High intensity statin.

- **Best to prevent CAD/MI : Statins (reduce LDL).**
- **Best to prevent Pancreatitis: Fibrate (reduce TGs)**

◀ Hypertriglyceridemia treatment

- **TG = <2** → No risk for anything, no treatment, lifestyle modification
- **TG = ≥2 to <5:** Use **statins** + omega-3 for CVS protection.
- **TG = ≥5 to <10: fibrate** to prevent pancreatitis,

L51- Thyroid disorders

◄ Hypothyroidism

◄ Causes

Primary	Secondary	Tertiary	Other
1- Hashimoto's thyroiditis (most common) 2- **RAI therapy** 3- Subtotal thyroidectomy 4- Excessive iodine intake 5- Subacute thyroiditis 6- **Iodide deficiency** 7- Congenital 8- Drugs: (lithium, amiodarone, antithyroid drugs)	1- pituitary adenoma 2- pituitary ablative therapy 3- pituitary destruction	Hypothalamic dysfunction	Peripheral resistance to thyroid hormones

◄ clinical presentation

•**Common features:**
-Easy fatigability, **coldness**, weight gain, **constipation**
-**Cool dry skin**, puffy face, hoarse husky voice,

•**GI tract:**
- **Chronic constipation**, ileus

•**CVS:**
- **Bradycardia, Decreased output**
- low voltage ECG, cardiomegaly, pericardial effusion

•**Renal:**
-Impaired GFR, water intoxication

•**Pulmonary:**
- Shallow slow respiration
- Respiratory failure

•**Anemia:**
-Impaired HB synthesis
- Iron/ folate deficiency
-Pernicious anemia

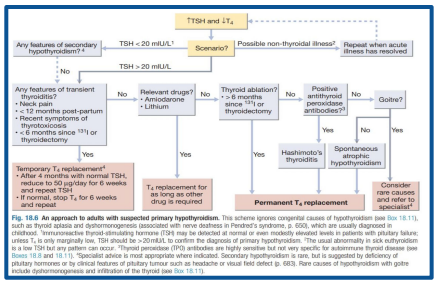
•**Neuromuscular:**
-Muscle cramps, paresthesia, muscle weakness, carpal tunnel

•**CNS:**
- lethargy, depression, agitation
-**Decreased concentration**

•**Reproduction:**
-Anovulatory cycles
-Menorrhagia

◄ Diagnosis

- **Serum TSH (initial test), high levels with clinical features confirms primary hypothyroidism**
- **Free T4 (confirms hypothyroid state)**
- **in Hypothyroidism (high TSH, Low free T4)**
- **Anti thyroid peroxidase (TPO) antibodies**



◄ Treatment

- **Thyroid replacement (Levothyroxine T4)**
- **follow up for serum free T4 and TSH**

◄ Complications

1- myxedema coma 2- myxedema and heart disease 3- hypothyroidism and neuropsychiatric disease

◄ Treatment of myxedema coma

-Acute medical emergency
-Three main issues: 1- Co2 retention and hypoxia 2- Fluid and electrolyte imbalance 3- Hypothermia
-if myxedema with heart disease, start treatment slowly then gradually increase it

Recommendations for the treatment of myxedema coma			
hypothyroidism	**loading dose of Levothyroxine** then daily maintenance	**hypocortisolemia**	intravenous hydrocortisone daily
hyponatremia	mild fluid restriction	**hypothermia**	blankets and **not active warming**
hypoventilation	intubation and mechanical ventilation	**hypoglycemia**	glucose administration
hypotension	**cautious volume expansion** with crystalloid or whole blood	**Precipitating event**	identification and elimination by specific treatment (eg: Antibiotics)

L51- Thyroid disorders

◄ Hyperthyroidism and Thyrotoxicosis

◄ Causes of thyrotoxicosis

1-**Diffuse toxic goiter (graves' disease)** 2- Toxic adenoma (plummer disease) 3- subacute thyroiditis
4- Hyperthyroid phase of Hashimoto's 5- Thyrotoxicosis factitia 6- others (Struma ovarii, TSH secreting pituitary adenoma, pituitary resistant to T3 and T4, metastatic thyroid carcinoma)

◄ Clinical features

•Cardiorespitatory:
-Dyspnea, Tachycardia
-**Atrial fibrillation**, high output cardiac failure

•Skin:
- **Warm with excessive sweating**
- pretibial myxedema
-pruritus, alopecia, thinning of the hair

•GI tract:
- **Diarrhoea**
- weight loss

•Eyes:
- **extraocular muscles dysfunction with** diplopia lid retraction, proptosis
-Periorbital swelling and conjunctival edema

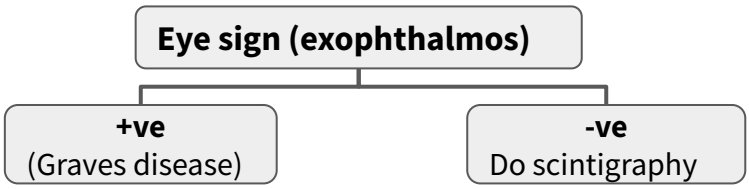
•others:
-Osteoporosis
-Irritability, anxiety, restlessness and psychosis

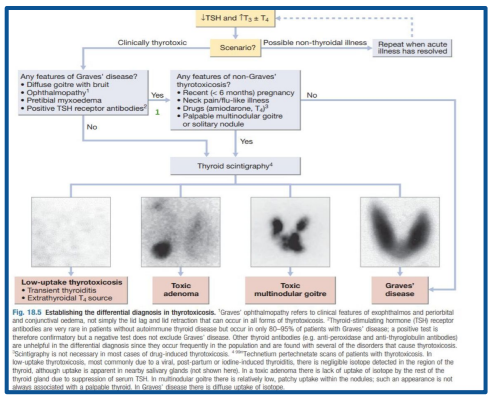
◄ Graves' disease (most common cause of Thyrotoxicosis)

-Autoimmune disease of unknown cause, affecting females more
-Most common features:
•Thyrotoxicosis •Goiter •Orbitopathy (**Exophthalmos**) •Dermopathy (**pretibial myxedema**) specific to Graves

◄ Diagnosis of Thyrotoxicosis

•Serum TSH, T4, T3 (initial test) shows: (Low TSH and High FT4)
•Thyroid stimulating Immunoglobulins (specific for and confirms Graves)
•Scintigraphy (RAI scan):
- Graves: Hot (diffuse increase uptake)
-Thyroiditis: Cold (reduced uptake)





◄ Treatment

1- **Antithyroid drug therapy** (propylthiouracil, carbimazole) should be started along with Beta blockers before iodine therapy or surgery to prevent thyroid storm
2- **Radioactive Iodine therapy** (^{131} Iodine is the most commonly used)
3-**Surgical Thyroidectomy** (subtotal thyroidectomy) when there is large goiter or failure of the previous two modalities

◄ Complications

1- **Thyroid storm** (precipitated by stress, infection or surgery)
Treatment: •Antithyroid drugs •Steroids •Beta blockers and fluids •Ipodate sodium

2- **Orbitopathy**
Treatment: •Steroids

3- in pregnancy
Treatment: - First trimester: Propylthiouracil
-Second and third trimesters: Carbimazole
- always keep T4 levels at the upper normal range

52- Obesity

Definition

Abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired.

Surrogate measures of adiposity

BMI:
Obese = BMI ≥ 30kg/m^2.
Relatively reliable except in:
Extremes of age or height & Very fit individuals with muscular build

Population	Risk of metabolic complications of obesity	
	Increased	Substantially increased
Caucasian (WHO)		
Men	>94 cm (37 in)	>102 cm (40 in)
Women	>80 cm (35 in)	>88 cm (35 in)
Asia (IASO/IOTF/WHO)		
Men		>90 cm
Women		>80 cm
China (WGOC)		
Men		>85 cm
Women		>80 cm

WHO recommended definition of obesity (2000)		
Classification	BMI(kg/m2)	Risk of comorbidities
Underweight	< 18.5	Low (but risk of other clinical problems increased)
Normal range	18.5 - 24.9	Average
Overweight (Pre-obese)	>25.0 25-29.9	Mildly increase
Obese (BMI >30)		
Obese Class I	30-34.9	Moderate
Obese Class II	<35-39.9	Severe
Obese Class III	>40.0	Very severe

Waist circumference (measure of visceral obesity):
The easiest way to assess obesity is by measuring the narrowest circumference midway between the lower border of the ribs and the upper border of the iliac crest.

Others: Ideal body weight, Anthropometric measures & Weight, in children: Growth Charts

Central Obesity

Central or visceral obesity is associated with more metabolic disease and complications:
- DM2 - Hypertension - Dyslipidemia

Measured by:
- Waist circumference - Waist:hip ratio - MRI - Single CT Slice(L4/L5) - DEXA
Waist:hip ratio of >1.0 in men and >0.9 in women is associated with ↑ risk of morbidity & mortality

Regulation of Appetite

Orexigenic factors (↑ Appetite):
- Ghrelin: Increase with hunger decrease with eating, Secreted primarily by the stomach and duodenum, and acts on hypothalamus to stimulate appetite

Anorexigenic factors (↓ Appetite):
- GLP-1 - Insulin - Leptin: Leptin from adipocytes acts on hypothalamus to decrease food intake and stimulate energy expenditure

Etiology & Pathogenesis:
- **Multifactorial**
- Biochemical/Dietary/behavioral/ Psychosocial/Genetic.
- Imbalance between energy intake and energy expenditure:
Calories consumed > calories used

Factors predisposing to obesity:
- Sedentary lifestyle - Diet (Overeating)
- Cessation of smoking - Sleep deprivation

Complications of Obesity

Metabolic:
- Cardiovascular (↑ BP, LDL & TGs ↓HDL, Impaired glucose tolerance & DM, Metabolic syndrome):
AACE recommends weight loss of 5% to 10% to reduce CVD risk

- DM2: Greater risk of developing T2D with higher BMI

- Others: NAFLD, Cancers (esophagus, colon, rectum, liver, gallbladder, pancreas) Infertility, Gout, Thrombosis & Gallstones.

Mechanical:
- Lung function: Reduced lung volume and vital capacity due to ↓ chest wall compliance.

- GERD & its complications: Barrett's esophagus, Erosive esophagitis and Adenocarcinoma.

- Obstructive sleep apnea: Weight gain increases severity of obstructive sleep apnoea

- Impaired physical function

Mental:
Anxiety, Depression, Suicidality & ↓ self esteem

Obesity and mortality:
Life expectancy ↓ as BMI ↑.
Obese patients are at risk of early death, mainly from diabetes, coronary heart disease (Major cause) and cerebrovascular disease.
- Weight reduction reduces this mortality and therefore should be strongly encouraged

52- Obesity

Screening

1. BMI measurement 2. Waist circumference 3. Evaluation of overall medical risks

Management

1. Lifestyle intervention: (Most important recommendation)

- Initial goal: 10% weight loss
- Rate of weight loss: Slow 1-2 pounds (0.5-1kg) per week, as rapid weight loss is associated with rapid weight gain, gallstones and electrolyte abnormalities.
- Aim for 4-6 months for weight loss, average is 8-10 kg loss
- After 6 months, weight loss is difficult due to Ghrelin & leptin effect + ↓ energy requirements

Physical Activity:
Start slowly, Avoid injury, increase intensity & duration gradually.
Increases body fitness, improves cardiopulmonary function, reduces stress, maintain weight loss & prevents weight regain

Long –term goal: 30-45 min or more of physical activity daily, 5 or more days per week

Diet therapy:
Indicated for all with BMI > 30 and those with BMI 25- 30 with comorbidities.
- Teaching about food composition (fat, CHO & protein) & calorie content by reading labels
Training: In selection of low fat, low carb foods.
Increase fruits & vegetables.
- Atkins diet: Good for short term under the supervision of a physician, but not for the long term.

2. Pharmacotherapy:

Indications:
- **BMI > 30**
- BMI 27-30 with comorbidities
- not for cosmetic weight loss

Used only when 6 months trial if weight & exercise fail to achieve weight loss

Note: Drugs can be used in the short term (up to 3 months) as an adjunct to the dietary regimen, but they do not substitute for strict dieting.

Liraglutide:
- GLP-1 receptor agonist
- loss of 15-18% of original weight maximum.

Simaglutide
- GLP-1 receptor agonist
- loss of 20-22%% of original weight maximum.

Orlistat:
- lipase inhibitor, reduces absorption of dietary fat
- Lowers Cholesterol (4-11%) & LDL (5-10%)
- loss of 8-10%% of original weight maximum.
- IMP side effect; Diarrhea

3. Surgical intervention (Bariatric surgery):

Indications:
- **Have BMI > 40**
- **BMI > 35 with comorbidities like**
  - **diabetes, sleep apnea, osteoarthritis, cardiomyopathy**
- **BMI 25-29.9 with WC > 102 cm in male and >88 cm in women**
- Age 18-60 & Psychologically stable
- **It can be used as a first-line option for individuals with a BMI > 50kg/m^2.**

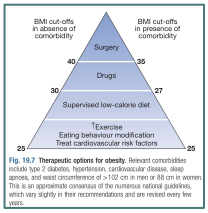


Fig. 19.7 Therapeutic options for obesity. Relevant comorbidities include type 2 diabetes, hypertension, cardiovascular disease, sleep apnoea, and waist circumference of >102 cm in men or 88 cm in women. This is an approximate consensus of the numerous national guidelines, which vary slightly in their recommendations and are revised every few years.

Types:

1. **Restrictive-type of surgery:**

Which restrict the ability to eat, for example:
- Adjustable gastric banding
- Vertical banded gastroplasty
- **Sleeve gastroplasty**

2. **Malabsorptive and restrictive**

Which reduce the ability to absorb nutrients, for example:
- **Roux-en-Y gastric bypass**

Gastric bypass causes more weight loss than sleeve gastrectomy, but sleeve gastrectomy is faster to do and with less malabsorption complications

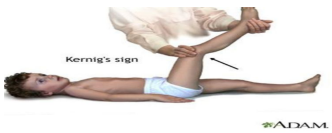
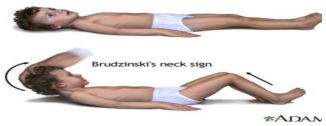
Bacterial meningitis

Definition

- Inflammation of the (meninges) pia mater and the arachnoid mater (dura mater is usually spared),with suppuration of the cerebrospinal fluid

Signs and Symptoms

- **Classic triad: fever, neck stiffness and confusion.**
- **Severe Headache, Photophobia** (intolerance of light) and Phonophobia (intolerance to loud noises) can be specific to bacterial meningitis.
- Bulging fontanel in infants, sometimes with hydrocephalus

Kernig's sign	Brudzinski's neck sign
While patient is lying supine, with the hip and knee flexed to 90 degrees pain limits passive extension of the knee.  The Kernig sign	Flexion of the neck causes involuntary flexion of the knee and hip.  Brudzinski sign

What's the most useful sign?

- **Jolt accentuation maneuver:** ask patient to rapidly rotate his or her head horizontally: Headache worsens, In healthy individuals it might be uncomfortable but a pt with meningitis will avoid doing it.
- **Sensitivity of 100%, specificity of 54% (Low, unlike kernig and Brudzinski signs),**

Management (Based on Dr notes)

How to manage a patient with meningitis?

- **Step 1:** Give empirical therapy!! Whenever you suspect meningitis or encephalitis, start empirical therapy! (In real life the pt will be started on empirical therapy in the ER, before you see him)
- **Step 2: CT** (To exclude herniation, supratentorial tumor, bleeding, pus collection (Subdural empyema) before doing LP bc it may kill the pt). **NEVER do LP before CT.**
- **Step 3:** LP.
  - **Contraindications to LP:** Herniation, Infection at the site of LP (e.g. Cellulitis), bleeding disorders, Low platelet count <100, anticoagulants . If one of these contraindication is present you can delay LP but **NEVER delay the treatment**

What antibiotics should be given?

- **Ceftriaxone + Vancomycin (**to cover highly penicillin resistant pneumococcus)
- Add ampicillin if there's suspicion of listeria

  Note: **Dexamethasone should be given** concomitant with 1st dose Abx to block TNF production

EXTRA

Typical CSF changes in viral, pyogenic and TB meningitis

	Normal	Viral	Bacterial	Tuberculosis
Appearance	Crystal clear	Clear/turbid	Turbid/purulent	Turbid/viscous
Mononuclear cells	<5/mm^3	10-100/mm^3	<50/mm^3	100-300/mm^3
Polymorph cells	Nil	Nil	200-300/mm^3	0-200/mm^3
Protein	0.2-0.4 g/L	0.4-0.8 g/L	0.5-2.0 g/L	0.5-3.0 g/L
Glucose	⅔ - ½ blood glucose	> ½ blood glucose	< ½ blood glucose	< ½ blood glucose

Special cases of bacterial meningitis

Meningococcal meningitis (Emergency)

Meningococcal meningitis and meningococcaemia: emergency treatment

Suspicion of meningococcal infection is a medical emergency requiring treatment immediately.

Clinical features:

- Petechial or nonspecific blotchy red rash
- Fever, headache, neck stiffness.

All these features may not be present – and meningococcal infection may sometimes begin like any apparently non-serious infection.

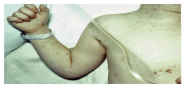
Immediate treatment for suspected meningococcal meningitis at first contact before transfer to hospital or investigation:

- Benzylpenicillin 1200 mg (adult dose) slow i.v. injection or intramuscularly
- Alternative if penicillin allergy – cefotaxime 1 g i.v.

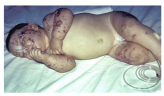
In meningitis, minutes count: delay is unacceptable. On arrival in hospital:

- Routine tests including blood cultures immediately
- Watch out for septicaemic shock.

- Fulminate meningococcemia with purpura caused by **Neisseria meningitidis**
  - Overwhelming sepsis, DIC
- **Classic: Meningitis with rash (Petechiae) + Headache + Fever**



- Lumbar puncture **should not be performed** if meningococcal sepsis is suspected because coning of the cerebellar tonsils may follow – the organism is confirmed by blood culture.



- **Treatment and prophylaxis:**
  - **Droplet Isolation:** 48h post Abx
  - **Treatment: Ceftriaxone or Pen G** 7 days
  - **Eradicate nasopharyngeal carriage:**
    - House hold contact
    - Health care providers who examined patient closely
  - **Prophylaxis (Not done routinely):** Rifampin 600 mg for 2 d or Ciprofloxacin 500mg once or Ceftriaxone 125mg I.M once

Recall: Ceftriaxone is C.I in neonates, give cefotaxime instead.

Listeria Monocytogenes meningitis

- **Pathology:** It causes brain stem, cerebellum inflammation (Rhombencephalitis) and meningitis
- **Risk groups:**
  - Age <1y or >50y
  - Alcoholics
  - Pregnancy: up to 30%
  - Immunocompromised 70 %
- **Routes of transmission:**
  - **Mainly food borne:** survives refrigeration
    - linked to poultry, hotdogs, cold cuts, coleslaw, ice-cream
  - **Cheeses,** particularly soft cheeses, have been implicated in listeriosis outbreaks worldwide.
  - Inform micro lab: special media **(Mueller-Hinton agar)**

Note: Whenever you see a pt with changing signals in brain stem and cerebellum MRI , think of Listeria.

- **Treatment:**
  - **Ampicillin** 2gm IV Q4h +/- Gentamicin 2mg/kg loading dose then 1.7mg/kg Q8h
  - **21 day** duration
  - Penicillin allergy patients: **TMP-SMX or Meropenem**

Neuro Brucellosis

- **Treatment:**
  - **Doxycycline**
  - **Plus** Rifampin
  - **Plus** Ceftriaxone 2gm IV q12h

What's the most common organism in neonates?

- Group B Streptococci (occurs ONLY in neonates)

What's the most common organism in older infants and children?

- Streptococcus pneumonia

What's the most common organism in adults?

- Streptococcus pneumonia

What's the most common complication?

- CN palsies (esp. deafness)

Aseptic meningitis

Definition

- Inflammation of meninges with sterile CSF
- **CSF: pleocytosis 100s,** Normal Glucose, Protein normal, Neg Culture

Note: Pleocytosis is the hallmark of aseptic meningitis, since it's sterile inflammation usually it has **neutrophilic** pleocytosis (there might be some lymphocytes, but the main cells are neutrophils)

Causes

- **Enteroviruses:** most common cause 80%
- HSV-2 (HSV-1 can cause it but it usually causes encephalitis)
- **Partially treated bacteria** (Think of it when the pt has taken abx in the past 2-3 days. When you suspect viral meningitis it is important to verify that the patient has not received antibiotics (for whatever cause) prior to the lumbar puncture, as CSF lymphocytosis can also be found in partially treated bacterial meningitis.)
- **Drugs: Metronidazole**, TMP-SMX, NSAIDs, carbamazepine (Given to epileptic pts), **IVIG-** headache is very common (Given to pts with myasthenia gravis and Guillain barre syndrome (GBS))

Viral encephalitis

General info

- **Encephalitis**: means acute infection/inflammation of brain parenchyma, and is often seen simultaneously with meningitis, usually viral.
- **Meningoencephalitis:** inflammation of brain + meninges
- In viral encephalitis, fever (90%) and meningism are usual; in contrast to meningitis, however, the clinical picture is dominated by brain parenchyma inflammation.
- **Personality and behavioural change** is a common early manifestation, which progresses to a reduced level of consciousness and even coma.
- **Seizures** (focal and generalized) are very common and focal neurological deficits, such as speech disturbance, often occur (especially in herpes simplex encephalitis).

What's the most common organism?

- **Most common: Herpes simplex (Either type 1 or 2)**:
  - How to confirm? Perform LP and PCR. MRI is also helpful (**The limbic system** and the medial temporal are its favourable place)
  - Treat with Acyclovir

Cerebral abscess

General info

- Bacteria may enter the cerebral substance through penetrating injury, by direct spread from paranasal sinuses or the middle ear, or secondary to sepsis. **Untreated congenital heart disease** is a recognised risk factor.
- Initial infection leads to local suppuration followed by loculation of pus within a surrounding wall of gliosis, which in a chronic abscess may form a tough capsule.
- **Organisms:**
  - **Streptococci (60-70%),** Bacteroides (20-40%), Enterobacteriacea (25-33%),
- **S&S:**
  - Fever, Headache, Meningism, Drowsiness
  - Seizures, raised intracranial pressure and focal hemisphere signs occur alone or in combination.

Management

- Lumbar puncture is potentially hazardous in the presence of raised intracranial pressure **and CT should always precede it.**
- **CT with contrast:** reveals single or multiple low-density areas, which show ring enhancement with contrast and surrounding cerebral oedema
- **CT brain:** If abscess more than 2.5cm then **surgical drainage**. And if patient neurologically unstable or decrease LOC drain regardless of size
- **Antimicrobials:** empirically Ceftriaxone with metronidazole, otherwise according to susceptibility

L54- Epilepsy

◄ Definitions:

- **Epileptic seizure:** **Transient** occurrence of signs and symptoms of sudden changes in neurological function due to **abnormal excessive** and **synchronous** discharge of cortical neurons
- **Epilepsy:** recurrent (two or more) **unprovoked** seizures.
- **Provoked seizures:** occurs in the setting of acute medical and neurological illnesses in people with no prior history of seizures

◄ Risk Factors:

- Febrile convulsion
- Family history
- CNS mass lesion and infection
- Perinatal insult, abnormal gestation or delivery
- Developmental delay
- Head injury
- Stroke

◄ Triggers for seizures:

- **Poor compliance**
- **Stress**
- **Infection**
- **Alcohol withdrawal**
- **Sleep deprivation**
- **Menstrual cycle**

Types of Seizures

Focal Seizures
preceded by warning "Aura"

- Simple partial seizures → **preserved** consciousness
- Complex partial seizures → **Altered** consciousness **but not** complete loss
- Partial seizures secondarily generalised

Generalized seizures
comes with **no aura** (no warning) and leads to **complete loss of consciousness**.

Unclassified seizures

Generalized Seizures

Absence (petit mal)	• Always start in **childhood**. They are mistaken for daydreaming or poor concentration in school. • Characterized by **fast recovery** from seizure (No post-ictal phase), and can be **provoked by hyperventilation**
Tonic-clonic "grand mal"	• **Rigid (tonic) and unconscious**, falling heavily if standing and risking facial injury. During this phase, breathing stops and central cyanosis may occur. • followed by **jerking (clonic)** movements emerge for 2 minutes at most. • Afterwards, there is a **flaccid state** of deep coma, which can persist for some minutes • During the attack, **urinary incontinence and tongue-biting** may occur. • Subsequently, the patient usually feels unwell and sleepy, with headache and myalgia.
Atonic "drop seizures"	Involving **brief loss of muscle tone,** usually resulting in heavy falls with or without loss of consciousness.
Myoclonic	Typically **brief, jerking movements,** predominating in the arms.

◄ Seizure approach

- **Non Invasive tests:**
  - Clinical history
  - MRI and Nuclear medicine
  - Neuropsychological evaluation
  - Video EEG
- **Invasive monitoring**

Typical EEG Sign	Localizes to	Typical EEG Sign	Localizes to
Oral Automatismes	Temporal lobe	Tonic arm elevation	Supplementary motor area
Hypermotor automatism	Frontal lobe	Epigastric Aura	Temporal lobe
Manual picking automatismes	Temporal lobe	Throat tightening Sensation	Insula
Visual Hallucinations	Occipital lobe	Ictal pain	Parietal lobe
Auditory Hallucinations	Temporal neocortex (Heschl's Gyrus)	Somatosensory sensations	Postcentral gyrus or Supplementary motor area
Olfactory Hallucinations	Mesial temporal lobe	Clonic activity	Precentral gyrus
Nystagmus, eye blinking, eye pulling sensation	Occipital lobe	De-ja-vu or jamais vu aura	Mesial / Medial temporal lobe
Ictal amaurosis		Fear	Most often temporal, but also frontal lobe

◄ Medical Treatment (first line):

MOA	1. **Reducing electrical excitability of cell membranes: by inhibition of sodium channel.** 2. **Enhancing GABA:** By inhibiting GABA-transaminase or direct GABA-agonist properties.
Clinical uses of Antiepileptic drugs	1. **Tonic-clonic (grand mal) seizures: phenytoin or valproate** (drugs of choice) 2. **Partial (focal) seizures: carbamazepine** (drug of choice) • valproate; clonazepam or phenytoin are alternatives. 3. **Absence seizures (petit mal): ethosuximide** (drug of choice) or valproate 4. **Myoclonic seizures: valproate** or clonazepam
Basic rules for drug treatment	• Drug treatment should be simple, preferably using one anticonvulsant (**monotherapy**). "Start low, increase slow" • **Add-on therapy** is necessary in some patients • If patient i**s seizure-free for three years, withdrawa**l of pharmacotherapy should be considered. Should be performed very carefully and **slowly!**
Drug resistant epilepsy	• Failure of at least **TWO** antiepileptic medications to completely control seizures ○ **Appropriately chosen for seizure type** . ○ Taken as prescribed ○ Well tolerated (not failed due to side effects)

◄ Surgical Treatment (second line):

- **Hemispherectomy:** one of the two cerebral hemispheres is removed.
- **Hemispherotomy:** disconnects the cortex of a hemisphere from the other cutting the corpus callosum.
- **Temporal lobectomy**

➔ **If the patient is not a good candidate for surgery?**

- ◆ Vagus nerve stimulation (NS)
- ◆ Deep Brain Stimulation (DBS)

◄ Status epilepticus

- **Definition:** recurrent convulsions that last for more than **30 minutes** **(5 min in the last update)** and are interrupted by only brief periods of partial relief.
- **Rhabdomyolysis** is a complication of SE that may lead to acute kidney injury
- **Treatment:**
  - Early status (up to 30 min): **lorazepam IV**
  - Established status (30–90 min): Phenytoin
  - If ongoing seizures: Phenobarbital, and Valproate
  - Refractory status (>90 min): general anaesthesia

◄ Epilepsy treatment in pregnancy

The **risk of teratogenicity** is well known, especially with **valproates**, but withdrawing drug therapy in pregnancy is more risky than continuation.

- All antiepileptic medications are not safe, however **lamotrigine** is the **safest**. .

◄ Seizures vs Syncope:

	Cardiogenic Syncope	Seizure Disorders
Loss of Consciousness	Typical	Common
Aura	-	+
Cyanosis	-	+
Episode Duration	Seconds	Minutes
Involuntary movements	Common	Typical
Amnesia	Yes	Yes
Postictal delirium & headache	-	+
Arrhythmia	Common	Rare
Electroencephalogram	Slow waves Flattening	Focal or General Spike
Responsive to AED	No	Often
Short Term Mortality	High	Low

L55- Peripheral neuropathies

	Weakness				Sensory symptoms	Severe proprioceptive loss	UMN signs	Autonomic symptoms/ signs	Diagnosis
	Proximal	Distal	Asymmetric	Symmetric					
Pattern 1: symmetric proximal and distal weakness with sensory loss	+	+		+	+				GBS, CIDP
Pattern 2: Distal Sensory loss with/ without weakness		+		+	+				CSPN[1], metabolic, drugs, hereditary: (CMT, Amyloidosis)
Pattern 3: Distal weakness with sensory loss		+	+		+				- Multiple: vasculitis, HNPP[2], MADSAM, infection (leprosy, lyme, sarcoid, HIV) - Single: Mononeuropathy, radiculopathy
Pattern 4: Asymmetric Proximal and distal weakness with sensory loss	+	+	+		+				Polyradiculopathy, plexopathy
Pattern 5 : Asymmetric distal weakness without sensory loss		+	+				±		- **LMN and UMN** - ALS - **Pure UMN** - PLS - **Pure LMN** - MMN[3]. PMA[4], BAD[5], LAD[6], MAMA[7]
Pattern 6 : Symmetric sensory loss and upper motor neuron signs		+		+	+	+	+		b_{12} deficiency, copper deficiency, friedreich ataxia, adrenomyeloneuropathy
Pattern 7: Symmetric weakness without sensory loss	±	+		+					- Proximal and distal SMA - Distal Hereditary motor neuropathy
Pattern 8: Focal midline proximal symmetric weakness	+ Neck/extensor + Bulbar			+ +			+ +		ALS
Pattern 9: Asymmetric proprioceptive loss without weakness			+		+	+			Sensory Neuropathy (Ganglionopathy)
Pattern 10: Autonomic dysfunction								+	HSAN[9], Diabetes, GBS, amyloid, poryphyria, Fabry's

L55- Peripheral neuropathies *(cont.)*

Ulnar nerve mononeuropathy	• **system involved: sensory and motor** • **clinical features: numbness of medial hand (fourth and fifth digits). weakness of abduction and adduction,** atrophy of intrinsic muscles of the hand, wartenberg and froment signs will be evident there will also be grip weakness • finger extensors are not involved (sign of radial nerve) •
carpal tunnel syndrome	• **system involved: sensory and motor** • **clinical features: wasting of thenar eminences. weak thumb abduction, reduced sensation over thumb, index, middle and ring fingers.** • **the most common focal neuropathy** • **it is usually asymmetrical, however, it can occur bilaterally.**
Hereditary neuropathy	• they might deny family history • sensory problems may not be present in the history but it can be present in the physical because it's chronic. • **clinical features: Deformities e.g. high arched foot (Pes cavus), symmetric weakness, distal more than proximal. absent reflexes. decreased proprioception, vibration, heat and pinprick.**
Diabetic neuropathy	• history of Diabetes • Clinical features: decreased sensation, numbness, and tingling that is progressive for a very long time (e.g 2 years) and pain • usually symmetrical. • most common Asymmetric neuropathy in Diabetics is Carpal tunnel syndrome • most common symmetric is Distal symmetric polyneuropathy.
S1 Radiculopathy	• **clinical features: Weakness of hip extension**, Weakness of knee flexion, Weakness of ankle plantar flexion, Absent ankle reflex. **sensory over lateral and plantar surfaces** • **How to differentiate sciatic from S1? by sensory distribution and the presence of hip extension.**
Common peroneal nerve damage	• **clinical features: Foot drop (difficulty in dorsiflexion). parasthesia in teh dorsum of the foot. toe dorsiflexion weakness. ankle eversion is also affected. inversion is NORMAL.** • **loss of sensation is well demarcated. over the dorsum extending over the lateral calf.**

Guillain barre syndrome	• **Paralysis follows 1-3 weeks after an infection**
	• signs and symptoms include:
	  ○ weakness of the **distal** limb muscles and/or **distal** numbness. (usually **symmetrical**)
	  ○ The weakness and sensory loss progress proximally, over several days **(acute)**
	  ○ Could be Motor, sensory, autonomic or combination
	  ○ **Loss of tendon reflexes**
	LP will show cytoalbuminologic dissociation (normal cells with high proteins)
	• **treated with IVIG or plasmapheresis NOT steroids**
	• **regularly motor pulmonary functions**
	• **CIDP is the chronic variant of the same presentation**

L56- Ischemic stroke

Stroke :

- Ischemic (blockage) → 80-85% of all strokes
- Hemorrhagic (bleeding) → 15-20% of strokes

Ischemic stroke :

- **Persisting neurologic deficit after 24 hours** and/or
- **infarct on CT or MRI.**

Transient ischemic attacks :

stroke-like symptoms that last for a very short time(<1hr) with complete recovery (most are <5 min) with the **absence of infarct** in neuroimaging study.

Risk factors:

Modifiable :

- **Hypertension. (Most important one)**
- **Diabetes mellitus.**
- **Hyperlipidemia.**

Non- modifiable:

- **Age**
- **Sex** young women are at higher risk than men due to pregnancy, hormonal changes.

Subtypes:

- **Blood vessels**
  - **Atheromatous (most common)**
  - Non-atheromatous
    - Vasculitis
    - Dissection of blood vessels (common in young patient "50 and less").
- **Heart**
  - Cardio Embolic
    - Atrial fibrillation
- **Blood**
  - Haemoglobinopathies
    - Sickle cell disease
  - Coagulopathy
    - Thrombophilia

Clinical presentation :

Middle cerebral artery occlusion:

- Hemiparesis: **Arm + face (UE) more than leg weakness (LE)**
- Hemisensory loss
- Higher cerebral dysfunction:
  - **Aphasia** if affecting the **dominant (left)** hemisphere.
    - **Broca's (expressive, anterior) aphasia: Damage in the left inferior frontal lobe** causes reduced speech fluency with relatively preserved comprehension
    - **Wernicke's (receptive, posterior) aphasia: Left temporo-parietal damage** leaves fluency of language but words are muddled. This varies from insertion of a few incorrect or non-existent words
    - **Nominal (anomic, amnestic) aphasia:** difficulty naming familiar objects
    - **Global (central) aphasia:** combination of the expressive problems of Broca's aphasia and the loss of comprehension of Wernicke's with loss of both language production and understanding. Writing and reading are also affected.
  - Neglect if affecting the **non-dominant** hemisphere.
- homonymous hemianopia

Anterior Cerebral Artery (ACA) occlusion :

Symptoms :

- **Weakness LE more than UE**
- Emotional disturbance.

Internal carotid occlusion:

Symptoms : above and ophthalmic

Posterior cerebral artery :

Symptoms:

- Vision - visual field (homonymous hemianopia)
- memory

Vertebrobasilar

Symptoms

- Cranial nerve syndrome with crossed motor
- cerebellum (cerebellar syndrome)
- altered LOC.
- homonymous hemianopia

Midbrain

Symptoms:

- CN III: signs of complete CN III palsy:
  - dilated pupil
  - Unilateral complete ptosis (levator weakness)
  - Eye deviated **down and out** (unopposed lateral rectus and superior oblique
- **Weber's syndrome:** Ipsilateral IIIrd nerve palsy with contralateral hemiplegia

Pons

Symptoms: CN V ⟶ Sensory:

- **CN VI ⟶ lateral rectus palsy**
- CN VII ⟶ facial weakness.

Medulla

Symptoms:CN VIII ⟶ vertigo, hearing loss.

- CN IX, X ⟶ dysphagia.
- CN XII ⟶ tongue weakness.

Small penetrating arteries (Lacunar syndrome)

Symptoms **:**

arms and face will be affected to the same degree.

no higher cerebral dysfunction or hemianopia

Pathophysiology :

- **Core:** area of irreversible damage.
- **Penumbra:** tissue at risk (ischemic but still viable cerebral tissue)
- Reduced blood blow (20-30cc) ⟶ tissue is still viable but stops functioning (penumbra) ⟶ needs to be saved ASAP
- A drop to 10 cc in blood flow ⟶ severe ischemia

History taking in Ischemic stroke :

- Onset (Last time seen normal)
  - Symptoms: FAST
  - Headache
  - Neck pain/ trauma in case of dissection
- Past Medical history
  - Oral contraceptives
  - Antithrombotics

Physical examination in ischemic stroke : :

- keep it neurological (focused) and quick, use **National Institution of Health Stroke Scale (NIHSS)**
- ABC (sometimes they add D for dextrose)
- BP Will be high (in both ischemic and hemorrhagic strokes)
- CN involvement and crossed motor typical presentation of brainstem strokes (ipsilateral CN involvement & contralateral weakness)
- Tone : **decreased** on side of weakness early on, **later on increased**
- Reflexes: hyperreflexia on side of weakness, with upgoing toe.

Investigations of ischemic stroke :

- Coagulation profile
- Chemistry : Fasting glucose
- Imaging
  a. CT scan : non-contrast CT is the only way to differentiate between ischemic and hemorrhagic strokes
  b. MRI :
     - MRI is **better overall, if immediately available**
     - MRI is used when there is diagnostic uncertainty or delayed presentation, and when more
- Vascular imaging
  a. Carotid U/S the least invasive
  b. CTA: invasive
- Cardiac workup : ECG to detect Afib

Management of ischemic stroke :

- Acute stroke management **code stroke**
  a. ABC
  b. Reperfusion
     - **Intravenous thrombolysis (IV t-PA): Effective up to 4.5 hours from onset.**
       - Exclusion criteria: **Intracerebral hemorrhage ,** stroke in the past 3 months., major surgery 14d,Pregnancy, active bleeding or acute trauma
     - aspirin (300 mg daily) should be started immediately after an ischaemic stroke **if the patient is not a candidate for thrombolysis.** If the patient has already received tPA, withhold aspirin for at least 24 hours.
       - In case of atrial fibrillation → add warfarin.
       - In case of significant carotid stenosis → surgery
       - In case of vasculitis → steroids
     - **Intra-arterial thrombolytic & Mechanical thrombectomy**
       - Only in case of blockage in **large vessels** e.g. MCA, ACA, Internal carotid or basillar
       - you could do for **up to 6 hours.**
     - **Internal carotid endarterectomy:** recommended in TIA or stroke patients with **internal carotid artery stenosis >70%.**
  c. Prevent progression and complications:
     - **BP and glycemic control**
       - **do not lower blood pressure abruptly in first week as it may reduce cerebral perfusion**
       - Control BP before thrombolysis bc of the risk of bleeding
     - **NPO, avoid aspiration.**
     - **Dx and Rx temp**
     - **PT, OT and early rehab.**
     - **DVT prophylaxis**

d. Other components of acute stroke management:

- Nutrition**:**If dysphagia persists for >48 hrs, start feeding via nasogastric
- Temperature: Control with antipyretics, **as raised brain temperature may increase infarct volume**

- **Long term stroke management:**
  a. Long term management of Risk factors (secondary prevention)
     - HTN: Transient hypertension, often seen in the first 24-48 hours following stroke, usually does not require treatment provided (let BP autoregulate) given diastolic pressure does not rise >100 mmHg, because high BP helps the cerebral circulation. unless
       - Patient is candidate for thrombolysis
       - patient has other risk factors that necessitate BP control
     - DM,Lipid , Smoking , A-fib, and Exercise

  b. Anti-platelet: for atherosclerosis Long-term soluble aspirin (75 mg daily)
  Anticoagulant
     - Heparin and warfarin should be given when there is:
       - atrial fibrillation
       - Hypercoagulability
     - Anticoagulants are potentially dangerous in the two weeks following infarction

  c. Rehabilitation

Transient ischemic attack :

- The term TIA traditionally also includes patients with **amaurosis fugax :** sudden transient loss of vision in one eye. the first clinical evidence of internal carotid artery stenosis – and forerunner of a hemiparesis.
- **Duration:** most TIA's **last 5-20 mins**
- **Features depend on: anterior circulation carotid system posterior vertebrobasilar circulation. system**
- **Prognosis: up to ⅓ will have a stroke (usually within 48 hours)**

Clinical findings :

Consciousness is usually preserved in TIA.
There may be clinical evidence of a source of embolus, e.g.:

- Carotid arterial bruit (stenosis)
- Atrial fibrillation or other dysrhythmia

Approach to TIA :

1. Needs **urgent assessment** (ER)
2. **Rule out other causes**
3. **Work up:** (labs, CT scan or MRI)
   - Vascular image of carotid CTA, MRA, US.
   - Cardiac work up: (EKG، echo, +/- holter)
4. **Start stroke prevention measures** (like ischemic stroke)

Hemorrhagic transformation :

- **> 50% of ischemic stroke have some hemorrhage**
- **Risk factors:**
  a. Older age
  b. Larger stroke size
  c. **Anticoagulant use**
  d. **Thrombolytic therapy/recanalization: increases the risk of haemorrhagic transformation**

Prognosis :

- **Why does hemorrhagic stroke carries worse prognosis?** Because the blood can compress the neurons, blood vessels. Also, it will cause edema and herniation

L57- Hemorrhagic stroke

Intracranial hemorrhage (ICH):

- meningeal space hemorrhage:
  - epidural hemorrhage.
  - subdural hemorrhage..
  - subarachnoid hemorrhage.
- intracerebral:
  - brain parenchyma.
  - IVH.

Risk factors:

- Hypertension. - excessive alcohol use. -smoking. -obesity. - physical inactivity. -older age.
- ethnicity/race. - medications (antiplatelet or anticoagulant). -sympathomimetics (cocaine & amphetamine in young age).

Etiology :

- Hypertensive ICH: 1- Essential: rupture of microaneurysms (Charcot-Bouchard aneurysm). 2- Eclampsia.
- Non-hypertensive ICH:
  1- Vascular malformation: aneurysm, cavernous hemangioma, bleeding disorders, venous and cavernous angiomas.
  2- anticoagulant (more than antiplatelets)
  3- Amyloid angiopathy: elderly especially Alzheimer pt. usually in cortical and subcortical areas (lobar area).
  4- Trauma: commonly causes subdural hemorrhage or epidural hemorrhage.
  5- Tumor
  6- Drug abuse: amphetamine, cocaine, and PPA.
- other causes:
  1- Cerebral venous thrombosis (CVT): young female due to OCP use.
  2- Intracranial neoplasm.
  3- Moya Moya.
  4- Vasculitis.

Pathophysiology :

- Primary immediate effect: hemorrhage growth and increase intracranial pressure.
- Secondary effect: downstream effect, edema, and ischemia.
- Site: basal ganglia, lobar regions, thalamus, pons, and cerebellum.

clinical presentation :

- **Alteration in level of consciousness**
- **Nausea and vomiting**
- **Headache**
- **Headache**

Investigations:

- LAboratory studies:
  - **CBC** → looking for thrombocytopenia.
  - coagulogram
- Imaging
  - **CT brain without contrast** (essential to differentiate ischemic from hemorrhagic)
    - Hyperdense signal intensity.
    - Multifocal hemorrhages suggests a traumatic etiology.
    - Hematoma volume can be approximately by (AxBxCx)/2.
  - **CT vessels:** CT angiography screening for AVMs, vasculitis.
- the workup:
  - MRI brain: with gado if looking for neoplasm, MRI diffusion-weighted.
  - MRA/MRV: if allergic to CT dye of if you're looking at venous outfkow.
    - MRA → for AVM and aneurysm.
    - MRV → for cerebral venous thrombosis.
  - Cerebral angiography.

Management of ICH:

- **Medical:**
  - **Control blood pressure:**
    - **Reduction of SBP to 140 is save.** why not less? to preserve blood perfusion to small vessel and preventing ischemia resulted from small blood vessel compression. in the area around the hemorrhage.
    - Use labetalol and/or nicardipine drip to titrate blood pressure.

Intracranial hemorrhage (ICH):

Management of ICH:

- **Medical:**
  - **Control blood pressure:**
    - Evidence-based practice nursing care:

    - Watch for neuro decline -Type and cross with your labs -Head of bed > 30o elevation -Head midline -Treat hyperthermia -Prevent vagal maneuvers -Control SBP (120-140) -Treat hyperglycemia -Treat hyperthermia -Seizure prophylaxis -DVT prophylaxis only after 48hrs & no haemorrhage
  - Cerebral edema: soduim (hypoosmolar hyponatremia) and CO2
    - Use the ventilator to manage CO2.
    - Get the Sodium levels up to 145- 155.
    - Mannitol 3% Given to prevent brain herniation that's caused by the cerebral edema.
      - Give them hypertonic saline e.g. 3% sodium or mannitol to lower edema
- Surgical:
  - Surgery never works except in only two scenarios:
    - Cerebellar hemorrhage if the hemorrhage is small we will observe the patient for any deterioration
    - Labor superficial hemorrhage: if small observe the pt deterioration to take him to the OR.

subarachnoid hemorrhage (SAH):

Etiology:

- Aneurysm rupture: usually **berry aneurysm rupture**, most common sites are: anterior communicating artery, posterior communicating artery, and middle cerebral artery.
  - Can be perimesencephalic SAH.
- Arteriovenous malformation (AVM).

Differential diagnosis of SAH:

- Migraine: presence of neck stiffness usually indicates SAH.
- Acute bacterial meningitis.
- Cervical dissection.

Clinical presentation:

- **Sudden acute severe headache:** thunderclap headache (often occipital), could be followed by vomiting and death.
- Other features: raised PB, neck stiffness or pain, straining, sexual excitement, papilloedema, and loss of consciousness at the onset.
- Physical examination:
  - Distress & Irritability. - Photophobia. -Positive Kernig's sign: (may take hours to develop).
  - Focal hemisphere signs, such as hemiparesis or aphasia.

Investigations:

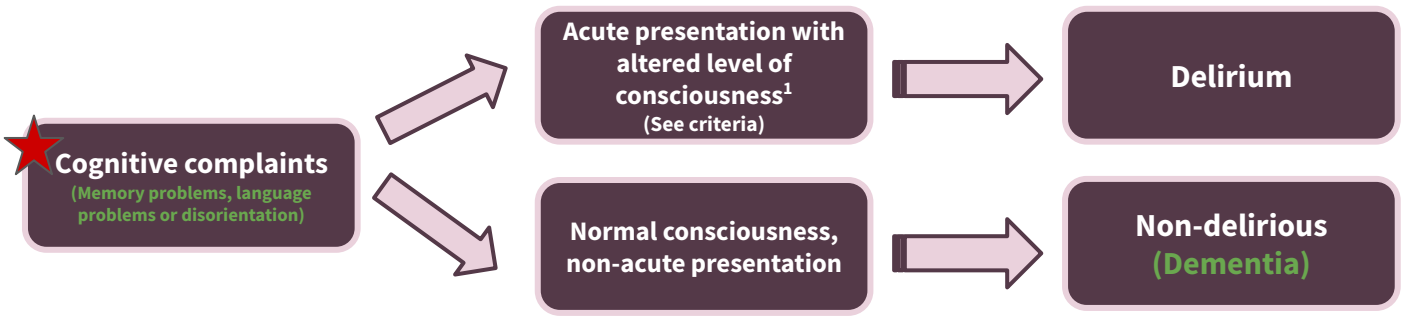
- CT brain scan: negative result does not completely exclude SAH
  - if CT is negative and the presentation is suggestive of subarachnoid hemorrhage then you do spinal tap to look for blood in the CSF.
- Lumbar puncture: performed 12 hr after symptom onset, to allow detection of xanthochromia → yellow CSF.
- CT angiogram: if wither CT of LP is +ve, angiogram is required to determine the optimal approach to prevent recurrent bleeding.

Management:

- Surgery: Coil/Clip
- Medication:
  - NIMOTOP/ NIMODIPINE: all the patient should be given, CCB prevent and treat the vasospasm, given for 21 days.
    - If patient develops vasospasm while on Nimodipine you should do angioplasty of the vasospasm.
- strict BP control.
- Check Sodium Levels → Treat the central Hyponatremia:
  - best managed by fluid restriction & 3% NaCl
- Check Urine output.
- Treat the obstructive hydrocephalus (a complication of SAH) → may require drainage via a shunt

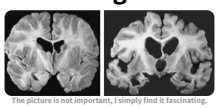
L58- Dementia

Characteristic	Delirium	Dementia
Causes	Metabolic, Toxic, Infectious, Drugs, Surgery & CNS disorders.	Vascular, Neurodegenerative, Infective, Toxic/Nutritional, Traumatic,Hydrocephalus, Inflammatory, Neoplastic & Prion.
Attention	Impaired (fluctuating (**worse at night**))	Usually alert
Onset	Acute (Hours/Days)	Gradual
Course	Fluctuating from hour to hour (waxing and waning)	Progressive deterioration
Consciousness	Clouded	Intact
Hallucinations/ Delusions	Present (often visual or tactile) Delusions of Harm	Rare, only in highly advanced disease
Diagnostic Criteria DSM-V	1) **Disturbance in attention** 2) **Change in cognition** 3) The disturbance develops **over a short period (usually hours to days)** and tends to **fluctuate** during the course of the day. 4) There is evidence from the history, physical examination, or laboratory findings that the **disturbance is caused by a direct physiologic consequence of a general medical condition**	1) **Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:** - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition 2) The cognitive deficits **interfere with independence** in everyday activities. 3) The cognitive deficits **do not occur exclusively in the context of a delirium.** **4) The cognitive deficits are not better explained by another mental disorder.**
Prognosis	Reversible	Irreversible
Treatment	Treat the underlying cause	Cholinesterase inhibitors



L58- Dementia *(cont.)*

Alzheimer's Disease
(Most common cause of dementia)

Clinical features	Risk factors	Pathophysiology	Diagnosis	Management
• **Decreased memory and new learning** • Language impairment • Apraxia • Unawareness of illness • Delusions • **Passivity** • **Delusions** • Depression, Circadian rhythm disturbances & Weight loss	• **Increasing age** • APOE ε4 • Down Syndrome • vascular risk factors(DM, HTN, Hyperlipidemia & Lack of exercise) • Brain trauma	• Accumulation of amyloid beta > **senile plaques** • Accumulation of hyperphosphorylated tau protein > **neurofibrillary tangles** • **Resultant loss of neurons and synapses, (esp. in basal forebrain leading to cholinergic deficit)**	• **Diagnosis is clinical** • **Brain structure on MRI may demonstrate medial temporal atrophy bilaterally** • **PET scans can demonstrate decreased metabolism in temporal and parietal regions** 	• **Donepezil, rivastigmine and galantamine which increase central nervous system acetylcholine** • Does not stop disease progression, only provides transient clinical stability. • Not a treatment, but education and **physical activity (Most beneficial)**

Lewy body dementia (LBD): dementia and signs of Parkinson's disease.
(Second most common cause of dementia)

Clinical features	Notes	Pathophysiology	Diagnosis	Management
• **Visual hallucinations** • **Parkinsonism** • **Fluctuations in cognitive ability** and **level of consciousness.** • **Visual spatial impairment** • **Sensitivity to neuroleptics** • **REM sleep behavior disorder** • **Autonomic dysfunction**	Parkinson's Disease Dementia (PDD) is similar to LBD, The difference is that a clear history of PD with NO cognitive impairment precedes the development of dementia by at least a year.	• **intracytoplasmic "Lewy Bodies" present in neurons, which are the result of abnormal α-synuclein protein accumulation**	• **Diagnosis is primarily clinical** • **PET scan may show decreased occipital lobe metabolism** • Myocardial scintigraphy may be abnormal due to abnormal cardiac sympathetic innervation	• Same as Alzheimer's Disease.

Frontotempol Dementia:
A number of different syndromes characterised by behaviour abnormalities and impairment of language.

Behavioral Variant	• Associated with personality changes, inappropriate social behavior (**disinhibited**), **lack of insight**, **Binging on certain foods**, **emotional blunting**, rigidity & decreased attention modulation. • MRI: **atrophy in the frontal lobes** (may be asymmetric).
Primary Progressive Aphasia	• Slowly progressive non-fluent aphasia: Patients present **first with a non-fluent type of aphasia.** • MRI : **focal left frontal atrophy**
Semantic Dementia	• Usually have **intact fluency, but comprehension is impaired** and decreased naming ability. • MRI may show focal **left temporal atrophy.**

Vascular Dementia

Clinical features	Risk factors	
• Frequently coexists with Alzheimer's disease	• Hypertension • Hyperlipidemia • DM • Smoking	• A single stroke in a region important to cognition such as **hippocampus or thalamus**, or a large stroke that affects multiple lobes. • **Recurrent strokes** that accumulate over time, there is a **step-wise development of cognitive deficits.** • **Slowly progressing cognitive** deficits due to subclinical progressing of **small vessel disease**.

Normal pressure hydrocephalus (NPH) (Rare)

Clinical features	Notes	Pathophysiology	Diagnosis	Management
Classically triad of: • **Gait impairment "magnetic"** • **Dementia** • **Urinary incontinence**	- In 2ry NPH, there is a history of a previous meningitis, inflammatory disorder, or SAH. - Idiopathic NPH is when there is no preceding explanation for the condition.	• **Impaired CSF absorption at the level of the arachnoid villi**	• **Improvement after a LP that removes 30-50 cc of CSF** • **MRI: dilated ventricles (CSF pressure is normal)**	• **CSF shunting procedure is performed.**

Creutzfeldt-Jakob Disease (CJD) (Rare, 1 in a million)

Clinical features	Notes	Pathophysiology	Diagnosis	Management
• **Rapidly progressing dementia, disease duration (usually 6 months).** • **Myoclonic jerks may occur.**	Prion disorder	• abnormally formed proteins that induce pathological transformations in other proteins leading to leading to spongiform pathology in brain	• **CSF Analysis: ↑ 14-3-3 protein** • **EEG shows characteristic periodic sharp wave complexes** • abnormal signal intensity in the basal ganglia and cortical ribbon	• **No treatment, patients die within a year.**

Feel free to vent here, no one will read it..

L59- Parkinsonism

◄ Types of movement Disorders

- **Hyperkinesia:** Myoclonus, Tremor, Dystonia and Chorea.
- **Hypokinesia:** Bradykinesia.

◄ Parkinsonism

- Clinical syndrome characterised primarily by bradykinesia, with associated increased tone (rigidity), tremor and loss of postural reflexes.
- **Most common cause is idiopathic parkinson's disease.**

◄ Idiopathic Parkinson's disease

Pathophysiology

- Presence of neuronal inclusions called **Lewy bodies** which contains tangles of α-synuclein.
- **Loss of the dopaminergic neurons** from the substantia nigra

Risk Factors

- Older age, men, pesticide exposure, MPTP (potent mitochondrial toxin) and non-smokers.

Clinical features

- Pre-motor → Ansomia, **REMBD**, autonomic dysfunction and Depression/anxiety.
- Motor →
  - **Bradykinesia**; **slowness of movement** and progressive **fatiguing**, **mask like semblance** of the face.
  - **Parkinsonian tremor** "pill-rolling"; rhythmic **oscillatory**, **predominantly at rest, re-emergence with maintained posture.**
  - **Rigidity;** "lead-pipe" "cogwheel", **independent of velocity.**
  - **Postural gait changes;** stooped posture, **shuffling**.
- Quit speech and drooling, **Visual hallucination.**

Diagnosis

- Clinical with normal imaging.

Management

Levodopa/Carbidopa (LD/CD)	Dopamine agonists (Pramipexole, rotigotine)	other drugs
- **Mainstay of treatment** - **Relieving akinesia and rigidity** - Combined with dopa decarboxylase inhibitor (carbidopa). - **ADRs**: ON-OFF phenomenon; ON with dyskinesia happens when the levels of L-dopa are too high.	- Used in combination with levodopa or as **initial monotherapy in younger patients < 65–70** with mild to moderate impairment. - Apomorphine: short-acting DA administered subcutaneously, It is used in advanced PD - **ADRs**: fibrotic reactions, including cardiac valvular fibrosis.	- (MAO)-B inhibitor: Selegiline - COMT inhibitors : Entacapone - Anticholinergic: help tremor, cause **confusion and cognitive impairment in older patients**.

Other management options

- Deep brain stimulation (DBS) → LD/CD responsive patients only) as an adjunct to treatment.

◄ Red flags

If present, suspect conditions other than Parkinson's disease.

- **Neuroleptic or anti-emetic drug use.**
- Early/prominent autonomic dysfunction
- Limited eye movements
- Pyramidal, cerebellar or sensory symptoms
- Cognitive impairment

L59- Parkinsonism *(cont.)*

◄ Other akinetic-rigid syndromes

Drug induced Parkinsonism	- **Metoclopramide** or haloperidol
Progressive Supranuclear Gaze Palsy	- Parkinsonism + the inability to look up & down due to degeneration in the part of the midbrain. - **Path**: Shrunken midbrain "**hummingbird sign**" and Tau deposition.
Multiple System Atrophy	- Cerebellar signs, extrapyramidal system and severe **early autonomic dysfunction.** - **Path**: α-synuclein inclusion and hot cross bun sign".
Vascular Parkinsonism	- Upper motor neuron signs, results from multiple strokes.
Corticobasal degeneration	- Cortical impairment: **Sensory, Astereognosis, Agraphesthesia, Apraxia.**
Wilson's disease	- Copper deposition occurs in the basal ganglia, the cornea and liver causing cirrhosis. - **Young patients <50** - Check serum copper and ceruloplasmin.

◄ Hyperkinetic disorders

Essential Tremor	- Hereditary, benign condition but impairing. - Slowly progressive, bilateral, asymmetric, upper limbs action tremor, that disappears at rest. - There is no bradykinesia, rigidity, or dystonia. - Cerebellar tremor could look exactly like an essential tremor. - Treated with **Propranolol**
Dystonia	- same movement happening persistently or repetitively, usually there's contraction of both agonist + antagonist muscles at the same time. - **Ballismus**: large amplitude choreiform movement, seen after subthalamic strokes usually, botulinum toxin injections or DBS may be useful.
Chorea	- continuous flow of random muscle contractions ('dance-like'). - Can occur in "Sydenham's Chorea" and in Huntington's disease (HD)
Myoclonus	- Involuntary single quick contraction of a muscle group (or its inhibition). Can be repeated but **not rhythmic**
Tics	- stereotyped movements or vocalizations (may be temporarily suppressed)

L60- Myopathies

Inflammatory Myopathies	**Polymyositis (PM):** inflammatory myopathy affecting the proximal skeletal muscles
	Dermatomyositis (DM): inflammatory myopathy that presents similarly to polymyositis, **with the addition of skin involvement**
	Inclusion body myositis (IBM)
	• **Skin features (Specific for DM):** Gottron papules, heliotrope rash, and the shawl sign
	• **Malignancies are associated with DM > PM**
	• Patients with IM typically complain of **muscle weakness** with difficulties reaching overhead, **climbing the stairs**, and/or **standing up**. Advanced disease may present with **dysphagia** and **aspiration** because of oropharyngeal muscle involvement, or even **respiratory failure** if breathing muscles are affected.
	• **DM** is primarily **distinguished** from **PM** by the **characteristic rash.**
	• **The best initial test is CPK and aldolase**
	• **Muscle biopsy is the pivotal investigation (most accurate test)!**
	  ○ **DM:** Perifascicular atrophy
	  ○ **PM:** No Perifascicular atrophy
	• **interstitial lung disease is strongly associated with the presence of antisynthetase (Jo-1) antibodies**
	• **Management: Steroids & screen for underlying malignancies**

Inclusion body myositis	**Inclusion body myositis (IBM):** inflammatory myopathy affecting both the proximal and distal skeletal muscles (mainly **Distal**). Common after **age 50** • **Quadriceps muscle weakness (Thigh):** knees lack support → frequent falling ○ Usually spares rectus femoris muscle • **+/- long finger Finger flexors:** difficulties gripping, e.g., shopping bags or a briefcase • **Severe Oropharyngeal dysphagia** • **Biopsy (most accurate test):** Inflammatory cells invading non-necrotic muscle fibers, Rimmed vacuoles. • Relentless progression, lacks effective therapies

Drug Induced Myopathies	• **Steroid myopathy:** due to chronic exposure to steroids
	  ○ Biopsy: type 2 fiber atrophy and lipid accumulation in type 1 fibers.
	• **Statin Induced Myopathy:** Statins inhibit HMG-CoA reductase, rate-limiting enzyme of cholesterol biosynthesis. Can cause:
	  ○ Discontinuation of the statin → resolution of symptom

Dystrophinopathies	• **They are x-linked recessive disorders** (manifest in males). **Duchenne** (**early** age) and **becker** (**late** age). • **Mutation** in the **dystrophin gene (Xp21)** → **absent** (in duchenne) or **reduced** (in becker) Dystrophin **DMD:** • **Symmetrical progressive (Proximal > distal) muscle weakness** (**Legs** & **Arms**) • **Course:** Onset age **2 to 5 yrs**, **Wheelchair** at **10/** • **Gower's sign, Loss of ambulation** at age 9-13 years, **Muscle hypertrophy: Especially calf** • **Dilated cardiomyopathy:** common after age 15 (usually the cause of death) **Becker:** • Older age at onset, Muscle weakness starts from > 7 yrs. Slowly progressive. "Becker is Better." Loss of ambulation usually in the 4th decade Investigations & Management: • Muscle biopsy: **absent dystrophin staining** (DMD). **Partial loss** of dystrophin staining (BMD)

L60- Myopathies *(cont.)*

Facioscapulohumeral dystrophy	• **Manifestations are Asymmetrical**
	  ○ **Face:** Initial manifestation, 95% you will detect it at the age of 30 with examination
	  ○ **Eyes:** Often early in disease course
	  ○ **Lid closure:** Incomplete
	  ○ **Sleeping:** With eyes open
	  ○ **Shoulder:** Pain in shoulder girdle, scapular winging, triple humb
	  ○ **Ear:** deafness
	• **Screen for:**
	  ○ **Hearing loss**
	  ○ **Retinal vascular disease**
	• **No screening** for cardiac needed unless symptomatic

Emery – dreifuss muscular dystrophy	• **Weakness: Humeroperoneal**
	  ○ Bilateral, Symmetrical
	  ○ Arms: Biceps & triceps; Deltoids spared.
	  ○ Scapular winging
	  ○ Legs: Late
	  ○ Face: Mild weakness or normal
	★ **Contractures occurs before weakness and it is often more limiting to function than weakness.**
	  ○ **in elbow, achilles tendon**
	  ○ **Spine:**
	  ■ Posterior neck (extension), Lower back: Usually later onset, but may present with rigid spine syndrome.
	• **Testing:**
	  ○ CK, EMG, **Cardiac screening for arrhythmia and cardiomyopathy (leads to sudden death)**

Myotonic Dystrophy	• The **most prevalent** inherited neuromuscular disease in **adults** (**Autosomal dominant**). • **Tandem repeats at DMPK gene (Anticipation phenomenon)** • **difficulty releasing hand grip on a doorknob or handle.** • **Frontal balding, Cardiorespiratory weakness** • **EMG:** myopathic plus **myotonic** discharges. Genetic testing (confirmatory test)
Malignant Hyperthermia	• **Triggered:** Anesthetics, Depolarizing neuromuscular blocking agents • **Clinical features:** Tachypnea, tachycardia, Rigidity, Acidosis ,Hyperkalemia Rhabdomyolysis, High CK, Hyperthermia. • **Treatment:** Remove anesthetic agent, Dantrolene sodium

Rhabdomyolysis	• Acute Syndrome of **muscle necrosis** due to extensive **injury** of skeletal muscle with **release of intracellular** muscle materials into the **circulation**.
	• **What is the commonest muscle disorder that causes myoglobinuria? Metabolic myopathies**
	• **Clinical features:**
	  ○ **Cola or tea color "dark" urine (Myoglobinuria)**
	  ○ **Elevated blood and urine myoglobin**
	  ○ Fever, **leukocytosis**
	  ○ Markedly **elevated CK**
	• **Complications: ↑ K+ → arrhythmia → death**
	• **Management: IV hydration** to **avoid** acute tubular necrosis (**ATN**) and **renal failure** !!!

L61- Multiple sclerosis

Multiple sclerosis	

Definition	• A chronic autoimmune, **T-cell- mediated**, inflammatory disorder of the CNS.
	  ○ **Myelin is produced by:**
	  ◆ **Schwann cells:** Peripheral nerves.
	  ◆ **Oligodendrocytes:** CNS
	• The most common chronic inflammatory, demyelinating and neurodegenerative disease of the CNS **in young adults**

Risk factors	• **EBV Infection:** Most common • **Vitamin D: Sun exposure & serum vitamin D are inversely related (**Sunlight may be protective**)** • **Smoking: also increase the severity of MS** • **Obesity & Genetics**
Epidemiology	• The life expectancy of patients **is reduced by 7–14 years.** • MS is the main cause of death in more than 50% of patients. Mostly due to MS complications e.g. aspiration pneumonia or Neurogenic bladder (→ Infections → sepsis)
Patho-physiology	**1.** **Characterized by breakdown of the blood—brain barrier (BBB)** → entry of **activated T lymphocytes &** other inflammatory cells nto the CSF **(1st change in MS)** **2.** Recognise myelin-derived antigens on the surface the microglia → **initiates destruction** of the oligodendrocyte–myelin unit **by macrophages** **3.** Most easily recognized **in the white matter** as focal areas of demyelination, inflammation, and glial (astrocytes) reaction → **Plaques** • Recurrent relapses lead to permanent myelin and axonal damage and oligodendrocytes loss

Pathology	• **Plaques of demyelination**, 2–10 mm in size, are the **cardinal features**.
	• Lesions are most easily recognized **in the white matter.** There has to be multiple lesions, if only one then it's not MS
	• **Plaques occur anywhere in CNS white matter but most commonly sites:**
	  ○ Optic nerves
	  ○ Periventricular region
	  ○ Corpus callosum
	  ○ The brainstem and its cerebellar connections
	  ○ Cervical cord (corticospinal tracts and posterior columns)
	  ■ **Spinal lesions:**
	  • **In MS: short** and **peripheral** (visualized on axial images)
	  • **In NMO: long** and **central** or circumferential.

Clinically isolated syndrome (Pre-MS)	★ **CIS is the first clinical episode that is suggestive of MS** • **Why don't we classify them under MS?** Bc it's only one episode and not all of them develop MS (Many ppl in their 20s may get this attack and then live normal for the rest of their lives) • Monophasic episode with symptoms and objective findings that reflect inflammatory demyelinating event in the CNS. • lasting for at least 24 hrs. (If less than 24hrs then it's NOT an MS attack) • Occurs in the absence of fever or infection • Resembles a typical MS relapse (attack) but occurs in a patient not known to have MS

L61- Multiple sclerosis *(cont.)*

Four main clinical pattern	**Relapsing-remitting MS (RRMS) (85–90%)** • **The typical and most common pattern of MS** • A purely RRMS is characterized by the **absence of worsening** neurological function outside of individual relapses • **The majority will eventually enter a secondary progressive phase** **Secondary progressive (SPMS)** • **Worsening irreversible** neurological function, **preceded by RRMS** that cannot be explained purely by worsening associated with ongoing relapses • This late stage of MS consists of **gradually worsening** disability progressing slowly over years. • Starting early treatment in RRMS can delay the onset of SPMS and hopefully even prevent it. **Primary progressive (PPMS) (10-15%)** • **Irreversibly continuous** worsening neurological function, **without preceding relapses** • Patients older at onset or with PPMS **have shorter survival.** Example: a 40 years old lady presenting with slowly progressing weakness in the lower limb. At first she was able to walk independently, then she depended on a cane to help her walk for months, afterwards she noticed that she needs a walker (bilateral support) to walk, which she kept using for a few months to years, and now she needs a wheelchair. **Relapsing–progressive MS (<5%).** • This is the least common form of MS. • It is similar to PPMS but with occasional supra-added relapses on a background of progressive disability from the outset.
Clinical feature of Multiple sclerosis	
Optic Neuritis ★	• **Blurred vision** usually in one eye. **NOT double vision**, seeing black dots, can't see clear in the dark. • **Pain exacerbated by eyes movement**. • Reduced perception of **colors**. (red desaturation, the color will be pale in the affected eye) • Flashes of light on moving the eyes. • Enlarged blind spot. because the optic nerve is inflamed and swollen **Note: Blurred vision in one eye + Pain on eye movement = Almost always optic neuritis**

Brain Stem Related Symptoms	• **Diplopia** if the nucleus of 3rd,4th and 6th nerves affected (the CNs themselves aren't affected, what's affected is their nucleus)
	• **Trigeminal neuralgia:** is a severe pain that happen when one of the divisions of V CN distribution is touched and lasts for a few seconds, happens if involve trigeminal nerve (sensory).
	• **Vertigo (spinning sensation) and nystagmus,** happens if there is a plaque in the cerebellum
	• **Facial numbness and weakness:** if the facial nerve is involved
	• **Internuclear ophthalmoplegia (INO): Bilateral internuclear ophthalmoplegia is pathognomonic of MS**
	  ○ A Specific gaze abnormality, characterized by impaired horizontal eye movement with weak adduction of the affected eye and abduction nystagmus of the contralateral eye
	  ○ Resulting from a lesion in the **medial longitudinal fasciculus** in the dorsomedial brainstem tegmentum of either the pons or the midbrain.
	  ○ If you see it in young patient almost always MS (If elderly, think stroke)

L61- Multiple sclerosis *(cont.)*

Clinical feature of Multiple sclerosis (Cont)	
Cerebellum Related Symptoms	• **Oscillopsia:** (A visual disturbance in which the object in the visual field appears to oscillate due to nystagmus) • **Dysarthria:** (Slurred speech) • **Imbalance:** (Wide-based gait)
Brain And Spinal Cord Symptoms	• **Lhermitte's sign: electric like sensation induced by neck flexion, very serious almost always indicate spinal cord lesion** (any **cervical** cord lesion, not specific to MS) • **Sphincter dysfunction.** urine incontinence, neurogenic bladder and stool incontinence**,** commonly seen if there is spinal cord lesion • **Cognitive dysfunction: memory, concentration, processing speed. (Uncommon in MS**,and usually does not happen with the first attack**)** • **Sensory loss/numbness/pain** • **Weakness (monoparesis, paraparesis, quadriparesis).**
Transverse Myelitis	• A general term that indicates inflammation of the spinal cord with cord swelling and loss of function. Typically, one or two spinal segments are affected with part or all of the cord area at that level involved • Spinal cord related motor, sensory &/or autonomic dysfunction. transverse in the name means involve more than one area of the spinal cord • **Sensory level,** means the is loss of sensation in a specific level eg. patient has complete loss of sensation from mid abdomen and below, this sign **indicate a spinal cord lesion**
Uhthoff phenomenon ★	• **Temporary worsening of pre-existing symptoms with increases in body temperature**, e.g. after exercise or a hot bath • Less than 24 h, Reversible if last for more than 24h think about relapse • It does not indicate that there's ongoing damage, it only indicates that there was an area of inflammation and demyelination

Diagnosis of MS: To diagnosis of MS you must have both:

Dissemination in time	Dissemination in space
• History of **at least two attacks** separated by at least one month. • **if 2 attacks occur in the same month it's counted as 1**	• Clinical evidence of involvement of **two CNS sites OR** of **one lesion with historical evidence of another site being affected.**

• **The presence of multiple lesions on MRI (dissemination in space) or the demonstration of additional clinical attacks on MRI (by showing lesions of different densities (dissemination in time)) fulfills the criteria for MS despite the presence of one attack in the patient's history** (enhancing are new, non-enhancing are old**)**

- **it is essential to ask about previous episodes of neurological symptoms**
- MRI is both the **best initial test and the most accurate test.**
- **Lumbar puncture and CSF analysis:** if you not sure about the diagnosis another way to confirm it is to do lumbar puncture and look for **oligoclonal IgG bands**, BUT **with presence of relapse and remitting symptoms.** Rarely used anymore

L61- Multiple sclerosis *(cont.)*

Management of MS

Acute treatment of relapses

- **Steroids (IV or orally Methylprednisone)**
- **Most of the time relapses resolve on their own but steroids shorten the relapse episode.**
- Only given when relapse is significant or affecting their life (e.g. a pilot comes with blurred vision = needs immediate attention = use steroids)
- **Plasma exchange** is used for those who don't respond to steroids

Disease modifying treatments

- Low efficacy DMT (eg: interferon, teriflunomide) vs high efficacy DMT (eg: natalizumab)

Examples:

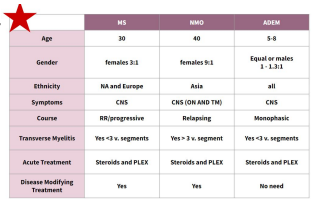
- **Patient with depression:** do not give interferon as it worsens depression
- **Patient with cardiac condition:** do not give fingolimod - causes heart block and seriously arrhythmias
- **Patient came with only tingling, no residual disabilities after the attack, few lesions on MRI→** give low efficacy DMT (interferon or teriflunomide)
- **Patient with only numbness, but had a previous relapse in which she described ataxia and difficulty walking, do we give her low efficacy DMT?** No (if u check MRI, you might find extensive lesions, multiple on spinal cord (very bad prognostic sign)) → start on fingo (medium efficacy DMT) or Natalizumab (high efficacy DMT)
  - **Natalizumab can cause:** Progressive multifocal leukoencephalopathy **PML (fatal) & leukemia**

Other Demyelinating Diseases

Neuromyelitis Optica Spectrum Disorder (Devic's disease)

- Characterized by longitudinally **extensive transverse myelitis (>3 segments)** and bilateral or recurrent optic neuritis.
- **Mean age is 10 years** later than MS.
- Affects mainly the optic nerves and the spinal cord
- **More severe attacks than in MS.** (presenting with **nausea**, **vomiting** and **hiccups** are important red flags in NMO)
- **Usually negative OCB in the CSF. While 90% of MS has positive OCB**
- **Serum antibodies to aquaporin-4 water channels on astrocytes are diagnostic** (should be done for every suspected case)

Acute Disseminated Encephalomyelitis



	MS	NMO	ADEM
Age	30	40	5-8
Gender	females 3:1	females 9:1	Equal or males 1 - 1.3:1
Ethnicity	NA and Europe	Asia	all
Symptoms	CNS	CNS (ON AND TM)	CNS
Course	RR/progressive	Relapsing	Monophasic
Transverse Myelitis	Yes <3 v. segments	Yes > 3 v. segment	Yes <3 v. segments
Acute Treatment	Steroids and PLEX	Steroids and PLEX	Steroids and PLEX
Disease Modifying Treatment	Yes	Yes	No need

- Acute monophasic demyelinating condition.
- **Frequently preceded by vaccination or infection.**
- **More common in children.**
- **Usually a monophasic illness (no relapses).**
- **Pathology:** Wide spread white and gray matter peri venous ''sleeves'' of inflammation and Axons are relatively spared unlike MS and NMO.
- **Symptoms: Encephalopathy, Multifocal neurological deficit, May fluctuates over a 3 months period for one single attack (If more than 3 months, it's not ADEM)**

Behçet's disease

- Behçet's principal features are recurrent **oral and/or genitalulceration**, inflammatory ocular disease (uveitis) and neurological syndromes.
- Brainstem and cord lesions, aseptic meningitis, encephalitis and cerebral venous thrombosis occur.
- There is a predilection for ethnic groups along the ancient 'Silk Road' – Turkey, the Middle East and Asia. Behçet's is associated with the **HLA- B51 allele.**

L62- Neuromuscular junction disorders (NMJ)

Neuromuscular junction physiology :

- This binding of ACh to ACh receptors in the motor end plate causes ion channels to open & so allow the sodium (Na+) ions to flow across (influx) the membrane into the muscle cell , generates a muscle action potential.

Classification of NMJ disorders :

1. According to the mechanism of action or etiology
   a. Immune mediated : Myasthenia gravis and lambert eaton syndrome
   b. Toxic / metabolic : Snake venom, Botulism, Organophosphates and Hypermagnesemia.
   c. Congenital : Congenital myasthenic syndrome
2. According to the location of the disruption:
   a. Presynaptic : decrease in the release of acetylcholine and impair the calcium channels
      - Lambert Eaton Syndrome , Botulism, and Congenital myasthenic syndrome
   b. Synaptic : Organophosphate
   c. Postsynaptic : The highest number of diseases affect the neuromuscular junction postsynaptically. either affects the Na+ channels or the ACh receptors : Immune mediated myasthenia gravis (most common)

Myasthenia gravis Definition :

The hallmark of the disorder is a fluctuating degree and variable combination of weakness in ocular either alone or in combination with , bulbar, limb, and respiratory muscles.

Epidemiology :

- Myasthenia gravis occurs at any age, but there is a bimodal distribution to the age of onset:

Pathophysiology of MG :

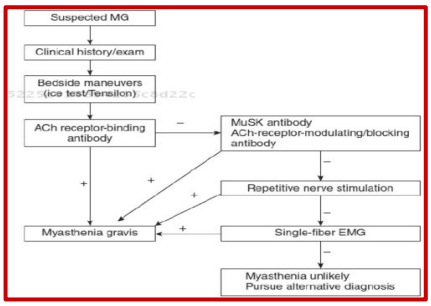
- In MG, there is reduction of postsynaptic AChRs due to production of anti-AChR antibodies that block receptors from binding to Ach and causes damage the postsynaptic membrane.
- Reduction in the number of AChRs available at the muscle endplate and flattening of the postsynaptic folds.
- Patients become symptomatic once the number of AChRs is reduced to approximately 30% of normal.
- Cause of fatigability in MS? **inefficient neuromuscular transmission (pathological) + presynaptic rundown phenomenon (normal)**
- **Which receptors are affected in MS? ONLY nicotinic** (skeletal muscles), while cholinergic (smooth &cardiac) are NOT affected.

Clinical features:

- >50% of patients present with ocular symptoms of ptosis (drooping of eyelids) and/or diplopia .
- half (80%) will develop generalized disease within two years.
- The distinguishing clinical feature in MG is fatigable weakness.
- Ocular myasthenia : The weakness is limited to the eyelids and extraocular muscles. Medial rectus muscle is usually most severely involved extraocular muscle
- Generalized disease : The weakness commonly affects ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles.
- maximum severity is usually in first year of disease, if After 2 years with no limb symptoms, disease usually remains purely ocular.
- Ocular muscles: **Asymmetric ptosis (fluctuating), binocular diplopia, and Pupils spared**
- Bulbar muscles
  - fatigable- prolonged chewing). Sometimes this can be severe to the extent that it will lead to jaw drop.
  - dysarthria , dysphagia and difficulty clearing secretions, and breathy nasal speech and nasal regurgitation
- Facial muscles
  - expressionless face, **Transverse smile,** and Weak eye closure
- Neck and limb muscles :
  - Neck extensor and flexor (Musk : NE>NF), Dropped head syndrome, Limb weakness: **Proximal > distal,** usually symmetric, and Wrist and finger extensors and foot dorsiflexors.
- Respiratory muscles :
  - orthopnea, and respiratory insufficiency and pending respiratory failure "myasthenic crisis

Investigations:

- Acetylcholine Receptor (AChR) Antibodies. (Best initial) :confirm the diagnosis.
- Anti- MuSK antibodies : If they were seronegative to antiAchR do anti Musk.
- SFEMG. (MOST SENSITIVE TEST)
  - Time required for EPP to reach threshold varies – JITTER
  - Sometimes EPP fails to reach threshold – BLOCKING
- Ocular Cooling/"ice-pack" Test .
- Edrophonium Chloride (Tensilon) Test, causes bradycardia
- Repetitive Nerve stimulation (RNS) :decline in the CMAP amplitude with the first four to five stimuli (characteristic decremental) response
- CT mediastinum : Thymic hyperplasia is most common 85%. **All patients should have a thoracic CT to exclude thymoma**
- Other Autoimmune disorders



Management of MG :

Symptomatic treatment (anticholinesterase agents) :

- Cholinesterase Inhibitors: **Pyridostigmine (Mestinon).**

chronic Immunotherapy:

- Prednisone (Main one), Azathioprine (Imuran),Mycophenolate (CellCept)

MG crisis (Rapid therapy):

- Plasma exchange and intravenous immune globulin [IVIG]

Refractory MG :

- rituximab

Thymectomy::

- Patient has thymoma Or Positive ACh receptor antibodies + Generalised MG + Young patient

Lambert-Eaton Myasthenic Syndrome (LEMS):

- Itis a rare presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine (ACh) is impaired.

Epidemiology :

associated with a malignancy, mainly **small cell lung cancer (SCLC).**

Pathophysiology :

1. Caused by an autoimmune attack directed against the voltage-gated calcium channels (VGCCs) on the presynaptic motor nerve terminal
2. Parasympathetic, sympathetic, and enteric neurons are all affected Ca++ channels.

Clinical features:

- Weakness/Fatigue (LL>UL) in Limb-Girdle Distribution ,weakness improves with use in LEMS
- slowly progressive proximal muscle weakness, particularly involving the legs
- Autonomic symptoms including **dry mouth**
- Post-tetanic potentiation: Recovery of lost deep tendon reflexes or improvement in muscle strength with vigorous, brief muscle activation is a unique aspect of LEMS

Diagnosis :

1. The diagnosis of LEMS is usually clinical and confirmed by the presence of antibodies to voltage-gated calcium channel (VGCC)
2. High frequency (10, 20 to 50 Hz) **repetitive nerve stimulation (**RNS) or brief (10 seconds) maximal isometric muscle activation result in **significant increment** (>60%, unlike MG in which there's decrement) with a marked **increase in the CMAP amplitude**

Treatment:

1. treat a primary underlying malignancy
2. Symptomatic therapies : These are guanidine hydrochloride, aminopyridines such as 3,4-diaminopyridine (3,4-DAP, aka Amifampridine), and acetylcholinesterase inhibitors such as pyridostigmine
3. Immunologic therapies include intravenous immune globulin (IVIG)

Botulism:

Clinical features:

- **Acute onset (Unlike MG) of bilateral cranial neuropathies associated with symmetric descending weakness.**
- initial GI symptoms (nausea & vomiting)
- Pupils dilated , Ptosis, and EOM
- Bulbar weakness, Limb weakness, and Respiratory weakness.
- **Absence of fever, The patient remains responsive**

Diagnosis:

Repetitive nerve stimulation (RNS) at low frequencies of 2 to 5 Hz causes decremental response.
RNS at high frequencies stimulation or exercise causes incremental response,
The amount of facilitation seen with botulism (40-100%) is usually less than that seen in Lambert-Eaton myasthenic syndrome (200%).

Treatment:

- antitoxin.
- Supportive.
- Equine serum heptavalent botulism antitoxin is used to treat children older than one year of age and adults.

Human-derived botulism immune globulin is used for infants less than one year of age

Tick paralysis:

- inhibits transmission at the neuromuscular junction by blocking influx of sodium ions In the postsynaptic membrane
- Symptoms include anorexia, lethargy, muscle weakness, nystagmus, and an **ascending flaccid**
- **paralysis.**
- The diagnosis of tick paralysis usually relies on the finding of a tick attached to the patient.
- Removal of the tick is the primary treatment of tick paralysis.

Snake venom :

- **Presynaptic junction toxin: beta-bungarotoxin** (krait) / mechanism: inhibit Ach release by inhibiting reformation of the vesicles after exocytosis /management: only supportive, no response to anti venom.
- **Postsynaptic junction toxin: alpha-bungarotoxin** / mechanism: toxins bind irreversibly to the acetylcholine receptor site / management: Antivenom

Clinical features:

- ptosis, ophthalmoplegia, dysarthria, dysphagia, and drooling.
- Weakness of limb muscles.
- **impaired coagulation profile.**
- The postsynaptic toxins produce findings on electrodiagnostic studies identical to those seen in
- myasthenia gravis, Repetitive nerve stimulation produces a decremental response

Organophosphate and carbamates toxicity:

- potent inhibitors of acetylcholinesterase, causing excess acetylcholine concentrations in the synapse.
- Commonly used as pesticides.

Clinical features :

- Both sympathetic and parasympathetic systems are involved.
- Symptoms include muscarinic signs and nicotinic signs .

Management & diagnosis:

- Emergency management (ABC management) often requires endotracheal intubation and volume resuscitation
- **Atropine** is used for symptomatic relief of muscarinic symptoms.
- It does not reverse the paralysis

Hypermagnesemia / hypocalcemia

- Causes inhibition of a acetylcholine release
- Magnesium has a calcium channel blocking effect.
- This produces proximal muscle weakness , ocular muscles are generally spread.

L63- Introduction To Cancer Diagnosis & Treatment

Cancer Definition:

- **A term used for diseases in which abnormal cells divide and escape the body control, these cells are able to:**
  - Invade surrounding tissues (benign tumors like lipoma and fibroma cannot invade. Locally malignant tumors like Osteoclastoma can invade locally but cannot send distant metastasis. The ture malignant tumors can both invade locally and send metastasis.).
  - Send distant metastases
  - Lose their functions.
- **Primary tumors:**
  - Represent de novo tumors in their initial site e.g. Breast cancer inside the breast tissue.
- **Metastatic tumors:**
  - Originate from the distant growth of the primary tumors to lymph nodes or other organs like liver, lung, bone, brain, etc..

Causes of Cancer

- **DNA Mutations:**
  - Cancer arises from the mutation of a normal gene.
  - Mutated genes that cause cancer are called oncogenes.
  - Radiation and other environmental factors (Tobacco, Alcohol, Radon, Asbestos, etc).
  - Random somatic mutations.
  - Inherited germline mutations.
- **Genetic Predisposition**
  - Retinoblastoma, p53 (tumor suppressor gene), APC, CDKN2A, BRCA1, BRCA2
- **Infectious agents**
  - **Viral:** HPV – cervical cancer, Hepatitis – liver cancer, EBV - Lymphoma
  - **Bacterial**: H. pylori – stomach cancer

Hallmarks of Cancer:

- Self-sufficiency in growth signals, Insensitivity to growth inhibitory signals, Absence of apoptosis, Limitless proliferative capacity, Sustained angiogenesis, Tissue invasion and metastasis.

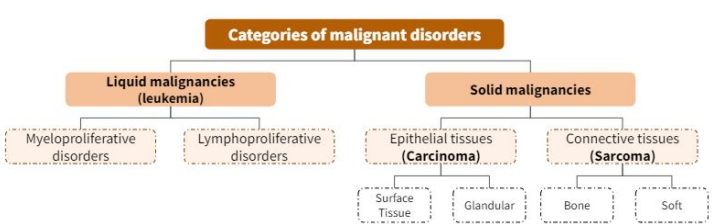
Q1: When to suspect cancer?

- Cancer Signs and Symptoms:
  - Cancer gives most people no symptoms or signs that exclusively indicate the disease.
  - Unfortunately, every complaint or symptom of cancer can be explained by a harmless condition as well.
  - **Do not forget the constitutional symptoms:**
    - Fatigue, fever, sweating, weight loss.
  - **What are the clues?**
    - Persistent, Progressive, Disabling and prevents it's patients from doing daily activity.
    - Symptoms & Signs changes according to the site of origin.
  - **Think about the pathology and site:**
    - The Mass is able to <u>invade locally</u> and <u>spread distantly</u> → To bone, brain, lung, liver .

Q2: How to diagnose cancer?

1	• **IT IS NOT A CLINICAL DIAGNOSIS**
2	• **IT IS NOT A RADIOLOGICAL DIAGNOSIS**
3	• **IT IS NOT SEROLOGICAL DIAGNOSIS**
4	• **IT IS A PATHOLOGICAL DIAGNOSIS**
5	• **IT IS A TISSUE DIAGNOSIS**

Categories of malignant disorders



L63- Introduction To Cancer Diagnosis & Treatment

Q3: What the essential work up for staging?

- **TNM** (T= tumor, N= Node, M= Metastases)
  - Clinical TNM
  - Radiological TNM
  - Pathological TNM
- **Radiology:**
  - XRay, MRI, CT, US, PET scan.
- **Surgical staging.**

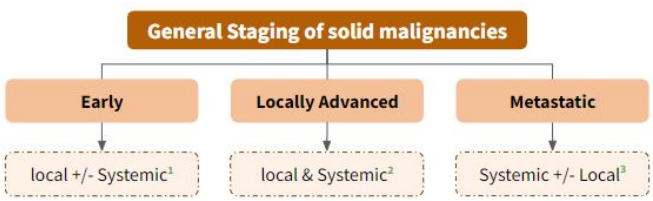
Q4: How to treat cancer?

- **Types of oncology problems:**
  - Patient with Suspected Cancer diagnosis
  - Patient with Established Cancer diagnosis (Answer the following questions):
    - Does the patient have cancer?
    - What type of cancer?
    - What stage of cancer?
- **Management Multidisciplinary:**
  - Surgery, Radiation, Medical.
  - Others Disciplines: Radiology, Pathology, Lab, Combined clinics, Tumor board.
- **Determine the treatment Objective:**
  - Either Curative or Palliative

Curative	Palliative
Therapy: • Aggressive, Expensive, recent, updated, complex. **Toxicity:** • Long term, irreversible	**Therapy:** • Simplest , Avoid hospitalization, Availability Least toxic **Toxicity:** • Short term, acute, quality of life

Different Treatment Modalities	
Local therapy: • Surgery & Radiation therapy	**Systemic therapy:** • Chemotherapy • Hormones • Biologicals • Immune therapy

- **Mechanism of Action of Immunomodulators**
  - Blocking the PD-1 or PDL-1 pathway would restore/promote the function of chronically exhausted tumor-specific T cells and decrease tumor-induced immune suppression
- **Liquid malignancies:**
  - Treated systemically
- **Solid malignancies:**
  - Treated according to stage



Q5: What is the prognosis of your patient?

- **What can medicine offer the cancer patient?**
  - The cancer type & extent (stage)
  - The host factors (age, sex, comorbidities)
  - The available tools

1 Tumors that can be cured	2 Tumors that can have prolonged survival	3 Tumors that can be palliated
• lymphomas, leukemia, early solid tumors.	• Locally advanced and some of the metastatic tumors.	• Metastatic solid tumors.

L64- Lymphomas

Lymphoma is a **cancer of the lymphatic system.** **It is of two main subtypes:**

	Hodgkin lymphoma	Non-Hodgkin lymphoma
Age	**aged 20-30 years** and **those 55 years of age**	**aged 60 years** and older. However, some types are more likely to develop in children and young adults.
Sex	**More common in males**.	**More likely in women** in most types.
Chemicals & Radiation	-	**Nuclear radiation and certain agricultural chemicals have links to non-Hodgkin lymphoma.**
Immunodeficiency	**HIV infection** can weaken the immune system and increase the risk	A person with a less active immune system has a higher risk.
Infectious factor	**Infectious mononucleosis:** The **Epstein-Barr virus (EBV)** can cause mononucleosis. This disease increases the risk of lymphoma.	Certain viral and bacterial infections that transform lymphocytes, such as the **EBV,** increase the risk. This virus causes **glandular fever**.

Grouping/ subtypes	• Nodular lymphocyte-predominant HL
	• Classical HL:
	  ○ **Nodular sclerosis HL (most common)**
	  ○ Lymphocyte-rich classical HL **(best prognosis)**
	  ○ Mixed cellularity HL
	  ○ Lymphocyte depletion HL **(worst prognosis)**
		• Indolent
		• Aggressive
		• Highly aggressive

Signs and symptoms

The definition, presentation, diagnostic tests, "B" symptoms, and staging of Hodgkin disease (HD) are the same as NHL. HD has Reed-Sternberg cells on pathology.

- **Painless swelling of lymph nodes (most common)**
- **B symptoms**: Persistent Fever without infection, Night sweats, Unexplained Weight loss and reduced appetite.
- Persistent fatigue
- Itchy skin
- shortness of breath

Diagnosis

- **Biopsy:**
  - **FNA: Tells you there is a malignancy but doesn't tell you what type.**
  - **Tru-Cut Biposy: This is the one used for the diagnosis of lymphoma because it gives you more details.**
    - **If biopsy is +ve, perform bone marrow aspiration/biopsy next (to make sure it hasn't reached the bone marrow).**
- **PET Scan: Before and after treatment, PET scan can differentiate between fibrosis/necrosis from treatment, and active cancer**

Staging

I	• Involvement of a **single lymph-node region or lymphoid structure.**
II	• Involvement of **two or more lymph node regions on the same side of the diaphragm**.
III	• Involvement of **lymph node regions on both sides of the diaphragm**.
IV	• **Extensive extranodal disease** (more extensive than "E").

L64- Lymphomas *(cont.)*

Staging (Cont.): Designations applicable to any disease stage	
A	• Asymptomatic
B One is enough	• **Fever:** > 38°, recurrent (Spiking up and down, not stable.) • **Night sweats:** Drenching (Excessive sweating), recurrent. • **Weight loss:** unexplained loss of >10% of body weight within the previous 6 months
X	**Bulky disease:** (If you see the letter X in the description of lymphoma → Bulky) • **Mediastinal:** ≥ 10 cm or > 1/3 internal transverse diameter at T5/6 on PA CXR. • **Non-mediastinal:** ≥ 5cm
E	• **Limited** extranodal extension from **adjacent** nodal site

Hodgkin's lymphoma (HL)		

Subtypes	• Nodular lymphocyte-predominant HL
	• Classical HL:
	  ○ **Nodular sclerosis HL (most common)**
	  ○ Lymphocyte-rich classical HL **(best prognosis)**
	  ○ Mixed cellularity HL
	  ○ Lymphocyte depletion HL **(worst prognosis)**	

Treatment	**Very favourable prognosis**	**Favourable prognosis in Stages 1A & 2A**
	• **Stage 1A NLPH, high neck NS & LRCHL.**	• **1-3 sites** • **Age ≤ 40** • **ESR < 50** • **Nodular sclerosis, Lymphocyte-rich classical HL**
	(Local radiation only)	**(Chemotherapy 3-4 cycles followed by radiation)**
	Unfavourable prognosis in Stages 1A & 2A	**Advanced stage**
	• **>3 sites** • **Age >40** • **ESR >50** • **Mixed cellularity**	• **Stages 3 & 4** • **B symptoms** • **Bulky disease**
	(Chemotherapy 4-6 cycles followed by radiation)	**6 cycles if stage A, 8 cycles if stage B. followed by radiation**

Feel free to vent here, no one will read it..

L64- Lymphomas *(cont.)*

Non-Hodgkin's lymphoma (NHL)

Clinical grouping

Indolent	• **Follicular lymphoma Grade 1,2. (Most common indolent).**
	• **Marginal zone lymphoma**
	  ○ Nodal
	  ○ **Extranodal (MALT): may regress with treatment of H.pylori**
	• Small lymphocytic lymphoma
	• Lymphoplasmacytic
	  ○ asociación with Waldenstrom's macroglobulinemia

Aggressive	• **Diffuse large B-cell lymphoma (Most common)** • Primary mediastinal large B cell lymphoma • Anaplastic large T / null cell lymphoma • Peripheral T cell lymphoma • Extranodal NK / T cell lymphoma, nasal type • **Follicular lymphoma Grade 3** • **Mantle cell lymphoma**
Highly Aggressive	Lymphoblastic lymphoma **Burkitt's lymphoma** Burkitt's like lymphoma

Treatment

Indolent lymphoma
e.g. Follicular Grad ½, small lymphocytic, marginal zone

Limited disease (Stage 1A, 2A if 3 or less adjacent node regions)	Advanced stage (some Stage 2, Stage 3, 4)
IFRT 30-35 GY **(Local radiotherapy only)**	• Palliative radiation therapy for localized symptomatic disease • Palliative chemotherapy for disseminated symptomatic disease • Observation only if low bulk, asymptomatic ○ Treat when symptomatic

Aggressive lymphoma
(e.g. Diffuse large B cell)

Stage I, some Stage II	Stage III, IV, B symptoms or bulky disease
(Chemotherapy 3 cycles followed by radiation)	**(Chemotherapy: 6 cycles if stage A, 8 cycles if stage B. followed by radiation, only if bulky disease or there is residual cancer)**

MALT lymphoma

Stage IE (H. pylori +ve)	Stage IE (H. pylori -ve or antibiotic failure)	Stage 2 or higher
• **PPI, 2 antibiotics (e.g. clarithromycin, amoxicillin) (H.pylori eradication)** • Follow up gastroscopy with Biopsy every 6 month for 2 yrs, then every 1 year	• IFRT 30 Gy (95% local control) **(Local radiotherapy only)**	• Treat as indolent lymphoma + H. pylori eradication

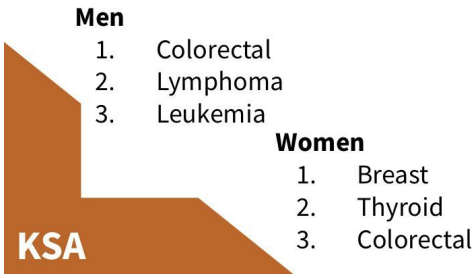
- **Stomach:** associated with **Helicobacter pylori infection** **Salivary Gland:** associated with **Sjogren's syndrome**
- **Thyroid:** associated with **Hashimoto's thyroiditis** **Orbital** (lacrimal, conjunctiva)

L65-Common solid tumors

◄ Classification of solid tumors

	Carcinoma	Sarcome	Germ cell tumor	Blastoma
Origin	**Epithelial cells**	**Connective tissue**	**Pluripotent cells**	Immature precursor **Embryonic tissue**
i.e.	Breast, prostate, lung, pancreas and colon	• Bone: osteosarcoma • cartilage: chondrosarcoma • fat: Liposarcoma • nerve	Testicular (seminoma), ovary (dysgerminoma)	Hepatoblastoma
Notes	Most common cancers	each of which develop from cells originating in mesenchymal cells outside the bone marrow.		Most common in children

◄ Cancer Statistics in KSA



◄ General principles of solid tumor treatments

- Early: Local & -/+ systemic
- Locally advanced: Local & systemic
- Metastatic: Systemic & -/+ Local
- Simple equation: Late presentation & Advanced stage= POOR OUTCOME. Early presentation+ Early stage= GOOD OUTCOME

Breast Cancer

Risk factors

- ❖ History of breast cancer
- ❖ Family history of breast cancer, especially in first-degree relatives
- ❖ Benign breast diseases / atypical hyperplasia
- ❖ Early menarche and late menopause
- ❖ Late first pregnancy and no pregnancy (Pregnancy suppress estrogen, and increase progestrone)
- ❖ Exogenous estrogens(HRT but not OCP)
- ❖ Radiation (HD) Hodgkin's disease

- **Self awareness(Monthly self exams):** Advised for all female >30.
- **Mammogram:** Every women aged 50-70, every 3 years.

Clinical features

- ❖ Painless lump or thickening of the skin (can be painful especially if infected.
- ❖ Thickening or swelling that persist.
- ❖ Nipple pain or retraction.
- ❖ Breast skin irritation or dimpling.
- ❖ Nipple discharge.
- ❖ Thickening or swelling that persist.

Staging of Breast Cancer

Stage 1 (early disease)	Stage ll (early disease)	Stage lll (locally advanced)	Stage IV (advanced)
Confined to the breast (**Node-negative**) (Tumor <2cm)	Spread to **movable ipsilateral axillary nodes (node-positive)** (Tumor 2-5cm)	Spread to the superficial structure of the **chest wall involvement** of ipsilateral internal mammary lymph node, or skin fixation, and/or **fixed axillary nodes**	**Metastasis** present at distant sites such as bone, liver, lungs and brain including supraclavicular lymph node involvement

L65-Common solid tumors *(cont.)*

Diagnosis:

➔ **Reasons to suspect breast cancer:**

Most common cancer in females, Wide age range 20 to +70y, Can occur during pregnancy & lactation, Can occur in pre, peri & post menopausal females.

What To do If you Suspect Breast Cancer?

- Do not just reassure the patient, Do not give hormonal therapy, Do not give antibiotics
- Take Careful history & physical examination:

If -ve: screening mammogram or US in young pt ➔ Suspicious? FNA

If +ve: Diagnostic Imaging Mammogram &US ➔ (Palpable mass/Equivocal or suspicious ➔ FNA.

- Perform Bilateral mammogram + breast US +/- Fine needle aspiration:

❖ Fine needle aspiration (FNA): The best initial biopsy. can differentiate between benign and malignant

❖ Core needle biopsy: Where cancer is considered likely, should follow FNA, assess for factors predictive of prognosis and response to treatment. These features include:

◄ Receptor status: ER, PR, HER2/neu, grade of tumour, Ki-67 proliferation index, molecular profiling.

❖ Open biopsy: The “most accurate diagnostic test” and allows for immediate resection.

Therapy (refer to the lecture for book details on breast cancer therapy)

1- Local therapy :

➔ Surgery

➔ radiotherapy

2- Systemic Therapy

➔ systemic therapy: (endocrine treatment and chemotherapy)

Indicated in: node-positive breast cancer, large primaries, oestrogen receptor-negative cancers and HER2 cancers .

➔ targeted: Hormonal and Biological therapy

Colon cancer:

Colorectal tube is a prime location for the development and growth of **small polyps or tumors.**

Risk factors

- Older age: older than 50 (Screening (**colonoscopy**) beginning at age 50).
- Personal history: colon cancer or adenomatous polyps, History of some other type of Cancer.
- Inflammatory intestinal conditions Ulcerative colitis and Crohn's disease
- Inherited syndromes Familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (also known as Lynch syndrome).
- Family history of colon cancer and colon polyps.

Other risk factors: Low-fiber, high-fat1 diet (most important) because it leads to **Chronic constipation,** A sedentary lifestyle, Diabetes, Obesity, Smoking, Alcohol, Radiation therapy for cancer.

Symptoms

- Change in bowel habit
- A feeling of bowel not emptying completely
- Unexplained Weakness or fatigue
- Unexplained weight loss, Unexplained iron deficiency anemia
- Persistent abdominal discomfort
- Rectal bleeding:

Left colon:fresh blood, present early.

Right colon: Occult blood, present with anemia.

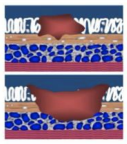
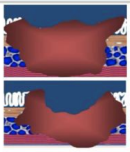
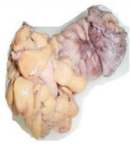
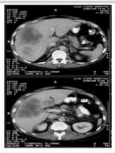
- **Post-menopausal females presenting with iron deficiency anemia should undergo a colonoscopy to rule-out colon cancer.**

L65-Common solid tumors *(cont.)*

Screening & early detection

- Population-based screening of people **over the age of 50 years** by regular faecal occult blood (FOB) testing
- **Colonoscopy: is the 'gold standard' for examination of the colon and rectum**
- other screening modalities: Flexible sigmoidoscopy: alternative option, CT colonography (imaging)

Staging

I	II	III	IV
Confined to wall	Beyond the wall	Nodal involvement	Metastasis
			
5 years Overall survival			
90%	60-80%	30-60%	<5%

Management

Depending on the location, options are:

- Surgery (mainly)
- Chemotherapy
- Radiation (if in the rectum)

Protective measures & prevention of colon cancer

- ❖ Decrease the risk: Vegetable, garlic,and fruits, Exercise, Milk, calcium consumption, Dietary fibre, Aspirin and other NSAIDs.
- ❖ Prevention: low-fat, high-fibre diet along with endoscopic screening.

Can we prevent Breast or Colon cancer?

Passive prevention :

- Discover Etiological factors Avoid theses factors eg. Smoking, Asbestos
- Avoid Breast cancer risk factors
- General health maintenance

Active prevention :

- Eliminate or prevent pre-invasive disease before invasion develops. (Chemoprevention,Surgery)
- Discover Pre malignant lesions Get rid of them before developing invasive cancer. (Colonic polyps & DCIS)

Feel free to vent here, no one will read it..

L66- Anemia

Definition: Anemia is a decrease in Hb in the blood below the reference level for the age and sex of the individual.

Mild anemia

- Few or no symptoms.
- Fatigue, Low exercise tolerance, SOB, palpitations, lightheadedness on arising, Sore tongue (glossitis), cracking mouth corners (angular cheilitis), peripheral paraesthesias (numb. toes..).
- **Clinical features:**
  - **Pica (pagophagia):** Desire to eat mud or ice. (in severe deficiency)
  - **koilonychia (with iron deficiency anemia)**
  - **Pallor**
  - **Neurological symptoms (severe B12/folate deficiency).**
  - **smooth tongue.**
  - **Orthostatic lightheadedness.**

Approach to Anemia

look at 3 CBC parameters and one additional test

1. The hemoglobin (Hb)
2. MCV (micro or normo or macro)
3. Reticulocyte count.

And the additional required test is the peripheral blood smear. Extremely important.

With the use of these 3 parameters your approach will be divided into 4 categories:

1. Low MCV (MCV <80 fL), **microcytic anemia.**
2. Normal MCV (MCV 80-100 fL)1 with low retic count, **normocytic anemia with inappropriately low bone marrow response.**
3. Normal MCV (MCV 80-100 fL) with high retic count, **normocytic anemia with appropriate marrow response.**
4. High MCV (MCV >100 fL), **macrocytic anemia.**

DDx of Anemia

MCV <80fL (TAILS)	MCV N, low retic count	MCV N, high retic count	MCV >100 fL[2]
1. Thalassemia[1] 2. Anemia of inflammation chronic disease[1] 3. Iron deficiency 4. Lead poisoning: Extremely rare 5. Sideroblastic anemia: Congenital, in paediatric	1. **BM failure:** a. Aplastic anemia: 2. **BM suppression:** a. Toxins, sepsis b. Organ failure: renal failure, liver failure, adrenal insufficiency c. Chronic inflammation d. Chronic diseases 3. **BM infiltration:** a. Lymphoma, leukemia b. Metastatic solid tumors c. Granulomatous disease (e.g.TB)	1. Bleeding 2. Hemolysis 3. Treated nutritional deficiency[3]	1. **Megaloblastic:** (impaired nucleic acid metabolism): a. B12 deficiency b. Folate deficiency c. Drugs: such as methotrexate and HU 2. **Non megaloblastic:** a. Liver disease b. Alcoholism c. Myelodysplasia (MDS) d. Thyroid disease (hypothyroidism)

Normal ranges in CBC

Test	Normal Range	Interpretation
Hemoglobin	Male: 13.5 (14)-17.5 g/dL Female: 11.5 (12.3)-15.3 (15.5) g/dL	**Low:** Anemia **High:** Polycythemia Hb 10 → mild Hb 7-10 → moderate Hb less than 7 → severe
Hematocrit (PCV) The volume of packed RBC in 100 ml blood	Male: 40-50% Female: 36-48%	
RBCs[1]	Male: 4.5-5.9 x10^6/mm3 Female: 4.1-5.1 x10^6/mm3	Measures the absolute RBC count: 1-**Low** 2-**Normal** 3-**High**
MCV	**80-96 IL**	**Low:** Microcytic **Normal:** Normocytic **High:** Macrocytic
MCH	34.4 ± 2.8 pg/RBC	**Low:** Hypochromic **Normal:** Normochromic
MCHC	34.4 ± 1.1 g/dL of RBC	**High:** Hereditary spherocytosis
RDW	**11.5 (11.7)-14.5%**	**High:** Increased: Many types of anemia (**Iron deficiency,** folate deficiency), liver disease
Reticulocytes	0.5-2.5% Males: 1.6 ± 0.5% Females: 1.4 ± 0.5%	
WBC	~4000-11000	**Low:** Leukopenia **High:** Leukocytosis *We are trying to avoid these terminology because they're not specific, you have to look for differential
ESR	2-12 mm/1sthour	

L66- Anemia *(cont.)*

Microcytic Anemia

Iron deficiency anemia.

Most common cause of anaemia in the world. Causes:

- Blood loss:
  - More common in female: heavy menses.
  - In males: always investigate for GI causes: Colon cancer, celiac disease(Most common in KSA).
- Increased demand: Growth, pregnancy.
- Decrease absorption
- Poor intake

Diagnosis

- Serum iron (Fe): Low.
- Ferritin level: The most accurate if it low (if high: exclude infection, because it's elevated in inflammation and infections.)
- Transferrin: the body produces transferrin in relationship to the need for iron, When iron stores are low, transferrin levels increase and vice versa.
- TIBC: Will be high

Treatment

- **Oral iron replacement** (ferrous sulphate or ferrous gluconate if patient has side effects)
- Parenteral iron replacement (In cases of malabsorption)
- Blood transfusion (If severe: Hb <7 g/dL)

Anemia of chronic disease

Etiology: Chronic infection, inflammation.

Pathophysiology

high levels of hepcidin expression play a key role. Cytokines released by inflammatory cells cause macrophages to accumulate iron and not transfer it to plasma or developing red cells. **Diagnosis:**

- Low serum iron but they are not deficient and don't need iron replacement, the defect is in the transportation.
- Low TIBC/serum transferrin.
- normal or raised serum ferritin.
- Peripheral blood smear usually reveals normocytic and normochromic anemia.'

Treatment: Correct underlying disease.

Normocytic Anemia: haemolytic anemias

Haemolytic anaemias are caused by increased destruction of red cells. any condition which leads to a reduction in the mean lifespan of the red cell is a haemolytic disorder.

How to differentiate between haemolytic anemia and anemia due to acute blood loss?

By clinical or laboratory findings, these 3 are haemolytic marker (high LDH and indirect bilirubin, low haptoglobin)

	Hemolysis	Bleeding
MCV	Normal or high	Normal or high
Retics	High	Normal or high
Bleeding	No	Yes, not always apparent
LDH	High	Normal
Haptoglobin	Low	Normal
Indirect bilirubin	High	Normal

L66- Anemia *(cont.)*

Normocytic Anemia: haemolytic anemias *(cont.)*

Diagnosis of haemolytic anemias

- Low Hb/Hct
- Elevated reticulocyte count
- Low haptoglobin (with intravascular hemolysis)
- Elevated LDH—released when RBCs are destroyed
- Elevated indirect (unconjugated) bilirubin

- **Autoimmune hemolytic anemia**

increased red cell destruction due to red cell autoantibodies. IgG or IgM labeled as "warm" or "cold" respectively. Cold hemolytic anemia often post-infectious, worsens with exposure of periphery to cold temperatures.

- **Diagnosis**
  - Coomb's test: Detects presence of either antibody on RBC.
- **Treatment:** Steroids/splenectomy– reduces immune function and RBC sequestration, respectively.

Lack of RBC enzyme makes cells very sensitive to oxidative stress the enzyme
G6PD oxidizing glucose-6-phosphate to 6-phosphoglycerate with the reduction of NADP to NADPH. The reaction is necessary in red cells where it is
the only source of NADPH, which is used via glutathione to protect the red cell from oxidative damage.

- **Sickle cell disease**

❖ one of the most common autosomal recessive gene defects.
❖ The specific Sickle cell mutation is substitution of hydrophobic valine for glutamic acid at position 6 of the beta-chain.

G6PD deficiency

Pathogenesis

In patients with sickle cell anemia, HbA is absent and completely replaced by HbS, whereas in heterozygous carriers, only about half is replaced.

Clinical features

- Anemia.
- Spleen: RBC destruction by the spleen، Splenic sequestration: Vaso-occlusion produces an acute painful enlargement of the spleen. Multiple infarctions: eventually leads to a fibrotic non- functioning spleen.
- Vascular features Arterial occlusion: leads to infarcts, pain crises, acute chest syndrome, stroke, MI, retinal and renal problems. Pulmonary hypertension
- Acute chest syndrome : pulmonary hypertension and chronic lung disease are the commonest causes of death in adults with sickle cell disease.
- Long-term problems: Growth and development

Diagnosis

Sickle solubility test: A mixture of HbS in a reducing solution such as sodium dithionite gives a turbid appearance because of precipitation of HbS, whereas normal Hb gives a clear solution.
Hb electrophoresis: always needed to confirm the diagnosis. There is no HbA, 80-95% HbSS and 2–20% HbF.
Management: Hydroxycarbamide (the first drug).

L66- Anemia *(cont.)*

Thalassemia

Characterized by hypochromic microcytic red cells

Beta Thalassemia

- **homozygous β-thalassaemia (major):** either no normal β chains are produced (β0) or β-chain production is very reduced (β+). There is an excess of α chains, which precipitate in erythroblasts and red cells causing ineffective erythropoiesis and haemolysis. The excess α chains combine with whatever β, δ and γ chains are produced, resulting in increased quantities of HbA2 and HbF

They are transfusion dependent, and they get iron overload and complication of it.

- **heterozygous β-thalassaemia:** Carrier of the trait "thalassemia minor" Or "thalassemia trait".

Beta Thalassemia major

Presentation: Prominent malar eminence and malalignment of the teeth, secondary to BM hyperplasia.
Extramedullary haemopoiesis (leads to hepatosplenomegaly and bone expansion → classical thalassaemic facies) chipmunk face. **Skull X-rays:** shows the characteristic 'hair on end' appearance.
Management : Long term folic acid supplements, regular transfusion: If transfusion requirements increase, splenectomy may help. The standard iron-chelating agent remains desferrioxamine
Ascorbic acid increases the urinary excretion of iron in response to desferrioxamine.

Beta Thalassemia intermedia

Symptomatic with moderate anaemia
Presentation: combination of homozygous mild β+- and α-thalassaemia leading to reduced α-chain precipitation(less hemolysis).

Alpha Thalassemia

- Often caused by gene deletions.

Four-gene deletion

- no α-chain synthesis and only Hb Barts (γ4) is present → Hb Barts cannot carry oxygen and is incompatible with life.
- Infants are either stillborn at 28–40 weeks or die very shortly after birth

Three-gene deletion (HbH disease)

- Has four β chains with low levels of HbA and Hb Barts.
- HbH does not transport oxygen and precipitates in erythroblasts and erythrocytes.
- Features: Moderate anaemia, Splenomegaly.

Two-gene deletion (α-thalassaemia trait)
One-gene deletion: blood picture is usually normal.

Iron Deficiency vs Thalassemia

	Iron deficiency anemia	Thalassemia
MCV	Low (80-70s)	Very low (70-60s)
RBC	Low	High or normal
RDW	High	normal
Ferritin/iron level	Low	High or normal

L66- Anemia *(cont.)*

Megaloblastic anemia

characterized by the presence in the bone marrow of erythroblasts with delayed nuclear maturation because of defective DNA synthesis(Megaloblasts).

B12 deficiency

Causes

1- Dietary: strict vegans.

2- Pernicious anemia:

- **Pathophysiology**: Autoimmune attack → atrophic gastritis & loss of parietal cells in the gastric mucosa → failure of IF production & achlorhydria → lack of B12 protection in stomach and gut → B12 malabsorption.
- **Investigations:** need to test if the IF is deficient: Antibodies against intrinsic factor, Anti- parietal cell antibodies, anti-IF antibodies

Clinical features: Neurological changes: only with very low levels of serum B1

Investigations

- Haematological: Features of megaloblastic anemia
- Bone marrow: megaloblastic erythropoiesis
- LDH: Raised
- Serum B12: usually low
- Schilling test

Treatment

- hydroxocobalamin.

Folate deficiency

- **Investigations:**
  - Serum folate: low (normal levels are 4–18 µg/L (5–63 nmol/L)).
  - Red cell folate level: The amount of folate in the red cells is a better measure of tissue folate.
- **Treatment:** daily oral folic acid
  - Correction of folate deficiency will correct hematologic abnormalities without correcting neurological abnormalities
  - Check B12 and correct first
  - Prophylactic folic acid in pregnancy prevents megaloblastosis in women at risk, and reduces the risk of fetal neural tube defects.

L67: Hypercoagulable state/ DVT

◄ Inherited hypercoagulable states:

- **Antithrombin:**
  - Antithrombin deficiency (e.g. in liver disease): Abnormality affecting the alpha 2 globulin (synthesized in liver) which helps neutralizing the activity of thrombin (IIa), Xa, XIa, XIIa and plasmin —> has a strong risk factor for VTE especially during pregnancy.
  - Antithrombin Functional Assays:
    - Antithrombin-heparin cofactor assay.
    - Progressive antithrombin assay.
- **Prothrombin:**
  - Prothrombin Gene mutation: resulting in elevated plasma levels of Factor II.
    - Genetic Test **(20210GA).**
  - Prothrombotic mutation (→ ↓ thrombin inactivation).
- **Protein C & S deficiency:**
  - Protein C and S inhibit activated cofactors Va and VIIIa, respectively.
  - Protein C is consumed and levels are low in vitamin K deficiency (both C & S are vit K dependent), DIC,liver disease, etc.
  - **Acquired Protein S deficiency may be induced by OCPs, pregnancy, or nephrotic syndrome.**
- **Factor V Leiden:**
  - Most common form of inherited thrombophilia, and Commonest cause of thrombophilia in West.
  - Activated Protein C Resistance.
  - FV Leiden → ↑ thrombin generation, (↓ anticoagulation) and ↓ inactivation of factor FVIIIa (also ↓ PAI inactivation → ↓ fibrinolysis).

◄ Acquired hypercoagulable states:

- **Antiphospholipid syndrome:**
  - Could be primary: sudden+extensive thrombosis OR secondary: e.g. SLE.
  - Clinical manifestation: Deep vein thrombosis, **early spontaneous abortions** (recurrent abortion), Livido reticularis.
  - Diagnostic criteria: presence of <u>at least one of the clinical criteria and at least one of the laboratory criteria</u>
    - Clinical criteria: Vascular thrombosis E.g. DVT, abortion, pregnancy complications.
    - Laboratory criteria: **Anticardiolipin antibodies** (IgG or IgM), **Lupus anticoagulant antibodies.**
- **Oral contraceptives and Hormone replacement therapy:**
  - Factor V Leiden + OCP – 50 x.
  - **increased factor VIIa levels** as well as **depressed antithrombin and protein S activity**.
- **Cancer:**
  - ↑ tissue factor.
  - ↑ procoagulant factor VIII and fibrinogen.
  - Compression/invasion of vessels.
  - **Hyperhomocysteinemia:**
    - Developmental delay, osteoporosis, ocular abnormalities, VTE, and severe premature CAD.
    - Increased arteriosclerosis.
  - **Pregnancy and postpartum:**
    - **Acquired prethrombotic state** in combination with **impaired venous outflow** because of venous compression.

L67: Hypercoagulable state/ DVT

◄ Hypercoagulable state/DVT:

- Clinical presentation:
  - Arterial: MI/Stroke.
  - Venous: DVT/PE.
- PE clinical presentation: Sudden SOB / sudden sharp chest pain (pleuritic) / hemoptysis / sweat+anxiety.
  - **PE with low BP (<90 mmHg) is called massive PE (IMPORTANT.)**

◄ DVT(deep vein thrombosis):

- Sign & Symptoms: leg (or arm) pain, tenderness, swelling, redness, and shiny skin.
  - Symptoms are neither sensitive nor specific for DVT.
- Risk factors: The presence of risk factors is a clue that VTE may develop or that it may already be present. (inherited + acquired).
- Investigation:
  - D-Dimer: Useful in low pre-test probability to exclude diagnosis of VTE.
  - Compression: direct approach, moderate to high pre-test probability.
  - Contrast venography (Golden standard): invasive
    - Non-invasive testing: Plethysmography, MRI, CT, V/Q scanning, Pulmonary angiography.

- Treatment:
  - Conventional Anticoagulation: **Heparin + warfarin is more effective than warfarin alone; all cases of VTE should be "bridged" with heparin.**
    - Heparin.
    - LMWH: Enoxaparin, Tinzaparin, Dalteparin.
      - Contraindicated in Dialysis dependent renal failure.
      - why is LMWH better than UFH?
        - Less risk of Heparin induced thrombocytopenia
        - No need for monitoring (UFH aPTT level is 1.5 times the mean of the control value which is 1.5- 2.5)
      - LMWH (SC) in stable cases of VTE but UFH (IV) needed in hemodynamically unstable patients or pts who need procedures.
    - Warfarin (Vit K antagonist):
      - **Inhibition of the vit K- dependent** Factor (II,VII,IX, &X) **1972.**
      - Monitor INR therapeutic INR 2-3 in most cases.
      - **Treatment continued for 3-6 months** mostly but longer or life long AC may be needed in recurrent cases of VTE.
      - **Treatment of choice for ESRF pt, prosthetic heart valves pt, and antiphospholipid syndrome.**
  - Direct Oral Anticoagulant (DOAC):
    - Direct thrombin (factor 2) inhibitor: Dabigatan.
    - Factor X inhibitors: Rivaroxaban, Apixaban.
    - **DOAC should now be the default choice for patients with DVT and/or PE.**
    - Advantages of DOAC: no need for bridging, no need for monitoring, smaller doses can be used as prophylaxis.

L67: Hypercoagulable state/ DVT

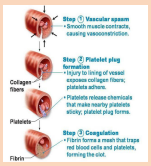
◄ DVT(deep vein thrombosis):

- Treatment:
  - Anticoagulants in VTE: Current Recommendation
    - Long-term therapy: usually 3 months
    - Longer time-limited period: Treatment longer than 3 months (6,12,24 months) but for a limited period.
    - Extended anticoagulant therapy: longer than 3 months (6.12.24 months) + continued indefinitely (for life).
    - For patient who has unprovoked VTE + low or moderate bleeding risk = extended anticoagulant therapy
    - For patient who has unprovoked VTE + high bleeding risk = long term therapy (3 months only)
  - **Overdose & Antidotes:**
    - For Heparin ⟶ Protamine sulphate.
    - For Warfarin ⟶ Vit K and fresh frozen plasma.
    - Idarucizumab for Dabigatrin.
    - Reverse for factor X inhibitors: Andexanet alfa.
  - Thrombolytic therapy: (reserved for massive PE), t-PA, u-PA, urokinase, alteplase.
  - IVC filters: Indicated in cases absolute contraindication + conventional anticogulation proven ineffective.
  - Thrombectomy (arterial).

L68- Bleeding Disorders

Overview of Hemostasis

Hemostasis



- The process through which bleeding is controlled.

Primary Hemostasis:
- Endothelium Injury
- Platelet plug
- Von Willebrand Factor

Secondary Hemostasis:
- Clotting Factors
- Soluble Protein Fibrinogen converted to insoluble Fibrin.

Lab tests

Platelet count (Normal: 150 – 400 x 10^9).
< 100,000 (Thrombocytopenia)
- 50,000 - 100,000 (Mild): Follow up
- < 50,000 (Severe): Needs intervention

- Platelets are produced in the Bone Marrow by fragmentation of the cytoplasm of megakaryocytes.
- **PLT Life Span (7 – 10 days).**

Prothrombin time (PT):
- Measures the effectiveness of the **extrinsic** pathway.
- NORMAL VALUE **(10-15 SECS)**

Partial Thromboplastin time :
- Measures Effectiveness of the **Intrinsic** Pathway.
- NORMAL VALUE **(25-40 SECS)**

Bleeding time :
- PROVIDES ASSESSMENT OF **PLATELET COUNT AND FUNCTION** NORMAL VALUE **(2-8 MINUTES)**

Thrombin time :
- A Measure of Fibrinolytic Pathway.
- NORMAL VALUE 9-13 SECS.

Bleeding disorders

Definition

- Bleeding disorders are a group of disorders that share the inability to form a proper blood clot. They are characterized by extended bleeding after injury, surgery, trauma or menstruation.

Primary hemostasis (only) disorders:
Characterized by Mucocutaneous bleeding - Petechial rash - Epistaxis - Menorrhagia.
Thrombocytopenia? First ask to examine the peripheral blood smear

Disease	Etiology	Diagnosis	Treatment
Quantitative			
Immune Thrombocytopenic Purpura (ITP)	- Primary: **Isolated thrombocytopenia** due to immune platelet destruction (auto AB to megakaryocytes) - Secondary.	**Diagnosis of exclusion.** • CBC (isolated thrombocytopenia) • PBS (large platelet) • Antiplatelet antibodies (Anti-GpIIb/IIIa)	**No bleeding**, count > 50,000: **NO treatment** **- 1st line:** • **Steroids & IVIG** **- 2nd line:** Splenectomy & Rituximab **- Refractory:** Romiplostim.
Qualitative			
Bernard soulier	Autosomal recessive Deficient platelet **GP**Ib-IX	Peripheral smear: Giant platelets • ↓ Platelets • Abnormal ristocetin cofactor assay	
Glanzmann thrombasthenia	Autosomal recessive Deficient platelet **GP**IIb-IIIa	Normal platelets Abnormal results on platelet aggregation testing confirm the diagnosis.	
Secondary or Drug induced	**Uremia (Renal disease)** drugs: e.g. aspirin or clopidogrel	•	Treat underlying cause Stop the drug.

L68- Bleeding Disorders *(cont.)*

Bleeding disorders *cont.*

Secondary hemostasis (only) disorders:
Characterized by hematomas, hemarthrosis, bruising, bleeding (mucosal, GI, GU, joint) deep bleeding.

Disease	Etiology	Diagnosis	Treatment
Hemophilia A	- Congenital: Inherited deficiency of **factor VIII** an **X-linked recessive disorder** - Secondary: Development of **autoantibodies** most commonly directed against **FVIII** (ass. with pregnancy, malignancy, advanced age).	• **Factor VIII Assay: low.** • Mixing study (corrected) • Normal VWF & PT.	• **Replacement of the deficient coagulation Factor** • **Desmopressin** • **Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid**
Hemophilia B	Inherited deficiency of factor IX; also called Christmas Disease; an **X-linked recessive disorder.**	• **Factor IX Assay: low** • Mixing study (corrected) • Normal VWF & PT.	
Hemophilia C	Inherited deficiency of factor XI ; also called Rosenthal Syndrome; an **autosomal recessive** disorder (Ashkenazi Jews).	• **Factor XI Assay: Low** • Normal PT & PTT	
Factor XIII Deficiency		• **Factor XIII Assay: FXIII Deficiency** • Normal PT & PTT	

Baseline factor activity level

★ **Severe Hemophilia** : defined as <1 % factor activity (<0.01 IU/mL).
★ **Moderate Hemophilia** : defined as a factor activity level ≥1 % of normal and <5 % of normal (≥0.01 - <0.05 IU/mL).
★ **Mild Hemophilia :** defined as a factor activity level ≥5 % of normal and <40 % of normal (≥0.05 - <0.40 IU/mL).

Disorders not specific to one step of hemostasis.
Clinical features: Bleeding of Mucous membranes, skin cuts, post-trauma or postoperative

Disease	Etiology	Diagnosis	Treatment
Von Willebrand Disease	**(most common bleeding disorder)** Defect of Von Willebrand Factor: Quantitative (type 1 & 3) | Qualitative (type 2) **Clinical features: Bleeding of Mucous membranes,** skin cuts, post-trauma or postoperative		
	Congenital: Autosomal dominant. **Normal function of VWF:** **- Mediate platelet adhesion.** **Acquired :**rare, caused by autoantibodies	Normal aPTT in (Type 1 & 2). Prolonged aPTT in (Type 2N, 2B, & 3) vWF: Ag. FVIII assay (low in 2N & 3). Plt count (low in 2M).	**- Replacement of exogenous vWF concentrate.** **- Desmopressin** **- Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid**
Disseminated Intravascular Coagulation	Trauma Septic shock Malignancy (esp APML) Major trauma	Prolonged PT and aPTT. decreased fibrinogen. Low plt. High LDH. Low haptoglobin.	- Treat underlying process . - fresh frozen plasma (FFP) - Cryoprecipitate

L68- Bleeding Disorders *(cont.)*

How to differentiate between bleeding disorders?						
Disorder	**Platelets**	**Bleeding time**	**INR**	**PT**	**aPTT**	**Other:**
Thrombocytopenia	↓	↑	**Normal**	**Normal**	**Normal**	-
Platelet dysfunction (e.g. aspirin therapy or uremia)	**Normal**	↑	**Normal**	**Normal**	**Normal**	-
Extrinsic pathway (e.g. Factor VII def.)	**Normal**	**Normal**	↑	↑	**Normal**	**Specific factor assay: Low** **Mixing study: correctable**
Intrinsic pathway (e.g. Hemophilia A, B & heparin therapy).	**Normal**	**Normal**	**Normal**	**Normal**	↑	-
Von Willebrand disease (vWD)	**Normal**	↑	**Normal**	**Normal**	**Normal/** ↑	**vWF assay: low (dominant)** **FVIII assay (low)**
Disseminated intravascular coagulation (DIC)	↓	↑	↑	↑	↑	-

Feel free to vent here, no one will read it..

L69- Acute & Chronic Leukemia

◄ Introduction

- A group of malignant disorders affecting the blood and blood forming tissues and results in an accumulation of dysfunctional cells because of a loss of regulation in cell division.

Clinical Manifestations	
Bone marrow failure	**Leukemic cells infiltrate patient's organs**
• Overcrowding by abnormal cells • Inadequate production of normal marrow elements • Anemia, thrombocytopenia, ↓ number and function of WBCs	• Splenomegaly • Hepatomegaly • Lymphadenopathy • Bone pain, meningeal irritation, oral lesions (chloromas)

Acute leukemias		
Overview	• **Acute leukemias** arise from the early stages of hematopoietic differentiation **(Immature cells).** • **Acute Leukemias carry high mortality but are CURABLE.** • **Abrupt onset.**	
Cell line	**Acute Myelogenous Leukemia (AML)**	**Acute Lymphocytic Leukemia (ALL)**
Characteristics	• Leukemia characterized by **proliferation of myeloid tissue** (as of the bone marrow and spleen) and an **abnormal increase in the number** of **granulocytes**, **myelocytes**, and **myeloblasts** in the circulating blood. • **One fourth of all leukemias and (85%) (90%) of the acute leukemias in adults**	• More common in children and adolescents than in adults. • It is the most common malignancy in children (25% of all cancers). • 15% of acute leukemia in adults • **Lymphadenopathy, Splenomegaly, Hepatomegaly & CNS: 15%**
Group	• **Adults | Males > Females**	• **Children | Males > Females**
↑Risk:	• Cytotoxic chemo, Radiation, Benzene.	• Trisomy 21 (Down syndrome) 15-fold ↑ in risk
Diagnosis	• **>20% blasts in peripheral blood or BM.** • **Blasts** either by morphology **(Auer rods)** or phenotyping with flowcytometry, IHC**,** cytochemical**: myeloperoxidase (MPO).** • **In Acute Promyelocytic Leukemia (APL) - (PML-RARA) (M3): t(15,17) using FISH.** **"ProMyelocytic Leukemia-Retinoic Acid Receptor α"**	• Flow cytometry on peripheral blood. • Acute lymphoblastic leukemia (**ALL**): **if >25% BM blasts.** • Acute lymphoblastic LYMPHOMA (**LBL**): if <25% BM blasts + mass lesion. • **Absence of granules/ Auer rods**
Management	• **Induction** (to achieve remission -defined < 5% blasts in a BM that is 20% or more cellular-): **Chemotherapy.** • **Consolidation** or "post remission" therapy: **Chemotherapy** or Allogenic stem cell transplant. **APL:** **Low risk: All trans retinoic acid (ATRA) + Arsenic (ATO)** **High risk: ATRA + Chemo ± ATO.** **Relapse? Autologous transplant.**	• ALL & LBL are the same disease & treated the same: • Induction 4-6 weeks > Consolidation 3 months > Late Intensification (re-induction) 3 months > Maintenance 2-3 years • **B-ALL** should be checked for **Philadelphia chromosome t(9,22); if positive TKI (Imatinib or Dasatinib) is added throughout therapy.** • All B-ALL should be checked for **CD20** and **if positive Rituximab should be added**. • Frequent IT MTX if documented CNS disease +/- cranial radiation.

L69- Acute & Chronic Leukemia

Chronic leukemias		
Overview	• **Chronic leukemias** arise from late stages of differentiation **(Mature cells)**	
Cell line	**Chronic Myelogenous Leukemia (CML)**	**Chronic Lymphocytic Leukemia (CLL)**

Characteristics	• Chronic, stable phase followed by acute, aggressive (blastic) phase
	• **Philadelphia (Ph) Chromosome → BCR-ABL gene**
	  ○ The chromosome abnormality that causes chronic myeloid leukemia (CML) (9 &22)
	  ○ Genetic marker
		• Most common adult leukemia in Western countries.

Diagnosis	• Typical findings in blood and bone marrow > then confirmed by the demonstration of the Ph chromosome by conventional cytogenetics, FISH analysis, or RT-PCR.	• CBC w/ diff → B-ALC >5000; "smudge cells" & small mature appearing lymphocytes w/ dense chromatin, scant basophilic cytoplasm Additional labs: • **Peripheral blood flow cytometry** → CD19+, CD20+ (dim), CD5+, CD23+, κ/λ restricted, surface Ig+ (dim), CD10– • BM bx unnecessary unless progressive cytopenias;
Management	• **Imatinib**: a Tyrosine-kinase inhibitor. • Stem cell transplant for selected patients.	• CLL is incurable • Indications for tx: Disease-related sx "active disease".
Complications		• Immunodeficiency, Autoimmune hemolytic anemia, Pure red cell aplasia, immune thrombocytopenia, Transformation..
Other Leukemias		
	Hairy Cell Leukemia: • 2% of all adult leukemias • Usually in males > 40 years old • Cells have a "hairy" appearance Multiple myeloma, Aplastic anemia,	Others: Myelodysplastic syndromes, Leukemoid reaction, Severe megaloblastic anemia, Lymphomas