Infectious diseases Review

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1. TB:

- 10% of infected people develop the disease > and 50% of them are contagious
- What increases the spread of disease:
    - **crowded living situation like prisons**
    - migration of people from endemic areas
- Factors that increase the risk of developing the disease after infection:
    - infecting dose
    - **host:**
        - **age: extremes of age (< 5 years old-elderly)**
        - **debilitating disease**
        - **HIV**
        - **DM, silicosis**
        - **Long term steroid use**
        - **poor nutrition, gastrectomy**
        - **alcoholism**
        - **infected within the past 2 years**
        - **CXR shows previous TB disease**
- Mode of transmission: airborne via droplet nuclei
    - **isolation: airborne isolation with –ve pressure room**
- Droplets expelled when person with infectious disease talks, sneezes, coughs,…
- **Most common organ involved is the lung and pulmonary TB is the most contagious**

- Pathogenesis:
    - **exposure** and inhalation of droplet nuclei
    - tubercle bacilli **multiply in the alveoli**
        - for most people it stops here
    - infect the alveoli > **immune system begins to fight**
    - 2-8 weeks: **macrophages ingest and surround the bacilli**> barrier shell (**granuloma**) > they're not killed but not multiplying
    - special immune system cells surround **and separate the infected macrophages**> mass from separated infected macrophages called **tubercle**
    - immune system cannot keep them under control **> multiply rapidly (disease)**> more lung tissue is destroyed and granulomas form > symptoms
        - granuloma can eat away at blood vessels > bleeding
    - enter the **blood stream** and **spread throughout the body** (miliary)
        - most likely to develop in: brain, larynx, LN, spine, bone, or kidney
- immunological features:
    - **requires cell mediated immunity**
        - multiplication proceeds for weeks until developments of cell mediated immunity both in initial focus and lymphohematogenous metastatic foci
    - **antibody response (B cells) has no role**
- microbiology: aerobic rods, non spore forming or motile & resistant to disinfectant

Latent	Active
Inactive, bacilli contained in the body	Active, multiplying
Healthy person > immune system controlled the infection	Unhealthy person > bacilli overwhelm the immune system
Bacilli remains in tubercle for years	Bacilli breaks out of tubercle > bloodstream
Granuloma may persist or breakdown to produce disease	Can occur after years of first infection or soon after
TST and blood tests +ve	TST and blood tests +ve
CXR is normal	CXR abnormal
Sputum smear and culture -ve	Sputum smear and culture +ve
Asymptomatic	Symptomatic
Not infectious	Infectious w/o treatment
Should consider treatment to prevent disease later on (INH for 6M)	---
No isolation needed	Airborne isolation in –ve pressure room
Not a case of TB	A case of TB

- People at risk of TB infection:
    - Close contact with TB patients (infectious)
        - **HC workers**
    - **Endemic areas**
        - Living, born, or visiting
    - **Residents or employees of residential facilities > crowding**
        - High risk congregate setting
    - **People with poor access to healthcare**
    - **People who inject illicit drugs (weaker immune system)**
    - **Elderly**
- Symptoms (pulmonary)
    - Fever, **night sweats**, weight loss, fatigue, and loss of appetite
    - **Cough (non productive > productive), hemoptysis,** and pain while breathing
    - Swollen LN and chills

    Signs: Rales on chest exam
- Primary:
    - **Infection of previously uninfected**
    - Few patients > self limiting febrile disease
    - Clinical disease occurs if:
        - **Hypersensitivity reaction**
        - **Progressive infection**
    - May occur after a latent period of **weeks to months**
- Post primary:
    - Exogenous or endogenous infection in a person **who has been exposed before**
    - **Apex**> high O2 > aerobe
    - Onset: insidious (**slowly progressive**) develops over weeks
    - **Radiology: ill defined opacity > consolidation > collapse and cavitation**
- Extra pulmonary TB:
    - LN: most common
        - Localized painless swelling
        - Common sites: cervical and supraclavicular
        - Early > discrete. late > matted +/- sinus
        - Dx: FNA (histology and culture) or whole excision biopsy (most accurate).
    - Pleural: presents as pleuritic chest pain.
        - **Pleural effusion (unilateral) and fever.**
        - Dx: both
            - **Thoracentesis: exudate**
            - **Biopsy: granuloma**
        - AFB rarely seen and culture 30% +ve

- Bone and joint:
  - **Source:**
    - **Reactivation of hematogenous**
    - **Spread from adjacent lymph node**
  - Common sites:
    - **Spinal: (pott's disease)**
      - Dorsal
      - Two vertebral bodies and **destroys the disc in between**
      - Advanced disease: **collapse fracture (more serious in higher lesions), kyphosis, gibbus deformity, paravertebral abscess (root pain)**
      - Dx: CT and MRI
        - **Accurate: biopsy (pathology, AFB, and culture)**
    - Knees and hips
- Meninges**: common in children**
  - Source: **blood or rupture of subependymal tubercle into subarachnoid space**
  - Symptoms: fever, N and V, headache, photophobia, and neck rigidity
  - **Evolves in 2 weeks**
  - Dx**: CSF studies**: AFB, WBCs, culture, glucose,…
- Peritoneum

- Conditions that make person more prone to extrapulmo TB:
  - Malnutrition
  - HIV
  - **Severe cases of pulmo TB**
    - **Primary lesion that progresses to clinical illness**
    - **Cavitating pneumonia**
    - **Lymphatic spread and lobar collapse > enlarged LN**
  - **Hematological dissemination**
- In children: asymptomatic states may cause miliary TB or **meningitis**
- HIV:
  - People with active TB are more frequent to have HIV
  - Presentation varies with stage:
    - Early: typical (upper lobe infiltrate +/- cavitation)
    - Late: diffuse infiltrate, intrathoracic lymphadenopathy, and no cavitation
  - Hard to diagnose:
    - Sputum is –ve in 40%
    - Atypical CXR
    - Negative PPD
- Drug resistant TB:
  - To one or more TB drug
  - Transmitted the same way and not more infectious

- Delay in detecting it may prolong period of infectiousness > delay in starting correct treatment
- **MDR: rifampicin and isoniazid**
- **XDR: rifampicin + isoniazid+ any quinolone + one injectable second line agent (amikacin, kanamycin, capreomycin)**

- Diagnosis:
  - History:
    - Symptoms of pulmo TB like cough for 3 weeks or longer
    - Symptoms of extrapulmo TB like
      - Hematuria (kidney)
      - Headache/confusion (meningitis)
      - Back pain (spine)
      - Hoarseness (larynx)
  - **Initial test:** **CXR**> abnormal > sputum
    - **Cavity in upper lobe**
  - **Sputum smear:** Ziehl-Neelsen stain > **AFB (gold standard)**
  - **Accurate: culture:**
    - All specimen even if smear on nucleic acid > -ve
    - Culture monthly until 2 consecutive –ve results (conversion)
    - **Lowenstein Jensen media (slow** growth 3-6 weeks)
    - **Liquid media BACTEC (4-14 days)**
      - expensive and time consuming
  - TST:
    - Read and interpret within 48-72 hours
    - Takes **2-8 weeks after exposure to work**
    - Off limited value because its **not sensitive nor specific**
      - **False +ve in:**
        - Non tuberculous mycobacteria
        - **BCG vaccine**
        - **False reading or wrong admin.**
      - **False –ve:**
        - Anergy
        - **Co-infection of any kind**
        - **Recent TB infection**
        - Extremes of age
        - Live virus vaccine
        - **Overwhelming disease or immunosuppressed**
        - RF, sarcoidosis, or lymphoid disease
        - Low protein states like in malnutrition
        - **Wrong admin.**
    - Measure indurated area across forearm (0 if non found)
  - **IGRAS: (interferon gamma release assay)**
    - Measuring immune response in the blood
    - **Doesn't differentiate between latent and active**
    - **Surveillance of who will benefit from treatment**

- **Used when testing patients who won't be able to return for reading or received BCG vaccine**
- Should not be used in children < 5 w/o TST

- **NAAT: (nucleic acid amplification test)**
  - DNA and RNA amplification
  - **Benefits:**
    - **Earlier lab confirmation, isolation, and treatment**
    - **Improve outcome (interrupt transmission)**
  - Perform 1 on each pulmo TB suspected case
    - A single negative doesn't exclude TB

- Management:
  - **Initial phase: INH, RIF, PZA, EMB daily for 8 weeks**
  - **4 months' continuation:**
    - **INH and RIF daily for 18 weeks**
    - **INH and RIF intermittently for 18 weeks**
- Why multiple drugs:
  - Rapidly reduce the number of viable organisms
  - Kill the bacilli
  - **Slow the rate of resistance**
- Drug failure:
  - **Non compliance (most common cause)**
  - Wrong drug or resistance
- Control and prevention:
  - Goals of program:
    - Detect early and promptly
    - Isolate and start treatment in persons with know/suspected TB
  - **Active TB:**
    - **Isolate for 2 weeks in –ve pressure room**
    - **Remains in isolation until 3 negative smears and clinical improvement**
  - **Treating LTBI:**
    - **High risk people with +ve IGRA or TST >/= 10 mm INH for 6 months**
    - **People with conditions that increase risk of TB**
- BCG vaccine:
  - Live attenuated of M bovis
  - C.I.:
    - Impaired immune response
    - Alkylating agents and antimetabolites
    - **PREGNANT WOMEN**

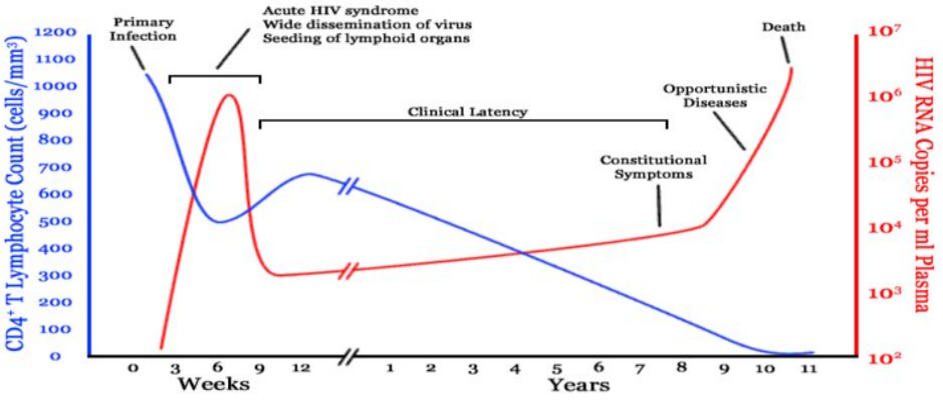
2. AIDS/HIV:

- HIV: infection with the virus that begins with
    - acute retroviral syndrome
    - transition to a multi year chronic illness that progressively depletes CD4 T lymphocytes critical for maintenance of effective immune function which ends up with life threatening immunodeficiency
    - progressive immunodeficiency
    - long latency
    - opportunistic infection
- RNA retrovirus
    - RNA > DNA in the host cell
- Types:
    - HIV 1: predominant world wide
    - HIV 2: predominant in western Africa
        - Slower progression to AIDS
- Main cells attacked by virus at CD4 T lymphocytes (helper)
- Hallmark of disease: progressive depletion in CD4 count
- Fragile virus that cannot live outside the body
- Found in semen, blood, vaginal fluid
- Transmission:
    - Sexually: mainly heterosexual
    - Vertical: mother to baby
        - Main mode of infection in children
    - Blood and body fluids: eliminated in developed countries
    - IV drug use
    - Does not spread by casual contact
- Structure of virus:
    - Icosahedral
    - Lipid envelope
        - External: gp120
        - Transmembrane gp 41
    - Nucleocapsid: p24 major core protein
        - Core contains two single RNA strands
    - Polymerase
- Life cycle:
    - **Binding** of **viral gp120 protein to CD4 receptors**
        - T cells, macrophages, microglial cells
        - Gp 120 and gp 42 bind to chemokines (co-receptors) CXCR4 and CCR5
    - **Fusion:** between cell membrane and the virion> Penetration> Upcoating.
    - **Reverse transcription**
        - Formation of cDNA
    - **Integration (by Integrase)**
    - **Transcription** of proviral DNA:
        - Genomic RNA
        - Structural mRNA Polymerase

- **Translation** of structural mRNA:
  - Formation of viral structural protein
  - Packaging of genomic RNA of structural protein
- Final **assembly**:
  - Insertion of viral specific glycoprotein into plasma membrane
  - Budding
  - Release of mature virions
- Final **maturation**: by cleavage of gag and pol by Protease enzyme

- Pathogenesis:
  - Early stage: massive replication of the virus in lymphatic tissue > viral reservoir containing proviral DNA are established in the latent T cell or macrophage

1. **Acute infection**: 1-4 weeks after transmission
   - Resembles infectious mononucleosis
     - Fever, malaise, lymphadenopathy, and skin rash (3days - 2weeks)
   - Symptoms resolve when RNA levels fall
   - CD4 count rebounds but remains below baseline
2. **Asymptomatic chronic phase**: active viral replication is ongoing and progressive
   - High RNA levels progress to symptomatic disease
   - Chronic immune activation > increase in various inflammatory markers
   - Increase in risk of co morbidities like CVD, renal dysfunction, and cancer
3. **Symptomatic phase (HIV infection):**
   - Immune system dysfunction



- immunologic staging: CD4 +ve T lymphocytes level is the main method of assessing the immune status of HIV +ve patient
  - ★ > 500: normal immunity
  - ★ 350-500: mild
  - ★ 250-350: moderate
  - ★ < 200: severe (AIDS)

❖ **Clinical manifestations:**
- Constitutional symptoms
- Skin: seborrheic dermatitis
- oropharynx: oral thrush, hairy leukoplakia, and mucosal Kaposi sarcoma
- Generalized lymphadenopathy (TB, **Non-hodgkin lymphoma**)
- Eyes: CMV retinitis

        - Genital:
            - condyloma acuminatum (warts)
                - HPV 6 or 11
                - Transmitted sexually
                - Diagnosis: clinically and confirmed with biopsy

4. **AIDS**
    - Marked CD4 cells fall **(<200)** > opportunistic infections and malignancy > death

- Natural history of disease:
    - 10 years for HIV to AIDS and then survival is 1-2 years (variable)
- HIV serology:
    1. transmission> acute infection> seroconversion: positive **antibody** test within 4 weeks and always by 6 months.
    2. asymptomatic infections: lasts a variable amount of time
        - avg 8-10 years accompanied by gradual decline in CD4 count
    3. Symptomatic (last 1-3yrs)> AIDS (avg survival 1-2yrs)

❖ **complications:**

- candidiasis: thick white coating
- TB: most common infection and leading cause of death
    - Pneumonia of the upper lobe
    - Due to cell mediated immunity
- Toxoplasmosis: spread primarily by cats
    - Meningoenchephalitis
    - Dx through serology and MRI
- Kaposi sarcoma:
    - Pink, red, or purple lesions of the skin and mouth
- Non Hodgkin lymphoma

- Screening:
    - Pregnant women
    - High risk groups
    - HC workers
    - Blood donors
    - Premarital tests
- Benefits of screening: early care and ART can prolong life and decrease chances of transmission
- Screening of patients aged 13-64
    - Separate consent not required
    - Should be notified that test will be performed
    - Screening recommended for all persons with STDs (syphilis, gonorrhea, and chlamydia)

❖ **Diagnosis:**

- **Combo test:**
    - Both type HIV1 and HIV2
    - P24 antigen
    - Antibody and antigen
    - Early detection
- ELISA: screening (detect only antibodies)

        - False –ves are high
    - Home testing kits only detect antibodies > doesn't detect acute
    - **Confirmation: INNO-LIA**
    - PCR (not routine)
        - Confirmatory test for undetermined cases
        - Assess viral load (treatment)
        - Babies born to HIV positive mothers
            - For several months their blood contains their mother's antibodies
        - Blood supplies
- Early management:
    - Reduce risk of transmission
    - Decrease morbidity and mortality
- Goals of therapy: can't be eradicated
    - Improve quality of life
    - Reduce morbidity and mortality
    - Restore immunologic function
    - Maximal and durable suppression of viral load
- **Opportunistic infection chemoprophylaxis:**
  when CD4 count is below 200:
    - Pneumocystis jirovecii
        - Co trimoxazole

  When CD4 count is below 50:
    - Mycobacterium avium intracellulare
        - Clarithromycin
- Indications of ART:
    - Symptomatic disease
    - Asymptomatic disease but CD4 count is less than 350
    - Pregnancy
    - Post exposure
- Prevention:
    - Abstinence
    - Safer sex
    - Circumcision (50% reduction)
    - Stop using IV drugs
    - Screen all blood donors
- Cornerstone of prevention is: education, counseling, and behavior modification
- Pregnancy:
    - In utero: 25-50%
    - Intrapartum (delivery): 60-75%
    - Breastfeeding:
        - Established 14%
        - Primary 29%

3. Healthcare associated infections:

Hospital Acquired Infections (HAI):

Are caused by infectious agents from endogenous sources such as skin, nose, mouth, GIT, and vagina or exogenous sources like HCW, visitors, medical devices and healthcare environment.

Four types

Catheter-Associated Urinary Tract Infections (CAUTI)

Most common type of HAI: > 30%

Pathogenesis:

Caused by Indwelling urinary catheters and often inappropriately indicated.

Microorganisms are either Exogenous via contaminated HCW hands during insertion, Or Endogenous from meatal, rectal, or vaginal organisms.

These organisms are protected by biofilms and we must remove the catheter to cure.

Diagnosis:

Must meet 1 of the following:

Fever, urgency, frequency, dysuria or suprapubic tenderness. With a positive urine culture.

Positive culture of a urinary catheter tip is not diagnostic.

Prevention:

Insert catheters for appropriate indications only as necessary and for the shortest time.

Aseptic technique for catheterization.

Closed drainage system.

Hand hygiene.

Avoid using catheters for management of incontinence.

Minimize use for those with high risk(women, elderly, immunocompromised).

Surgical Site Infections (SSI)

Second to CAUTI and causes 17-20% of all HAI.

Causes:

Inadequate antibiotic prophylaxis (Choice, time, or dose)

Incorrect/ineffective surgical site or skin preparation.

Inappropriate wound care(dressing).

Risk Factors:

Duration, type of wound, type of surgery, poor glucose control, hypothermia... etc.

Surgical wound classification:

I- Clean. II- Clean-contaminated

III- Contaminated IV- Dirty

		Types of SSI: Superficial incisional SSI occurs within 30 days and involves skin and subcutaneous tissue with lack of systemic symptoms. It is diagnosed clinically and a negative culture does not rule it out. Deep incisional SSI occurs with 30 days or 1 year if there is an implant. Has systemic manifestations and involves the deep tissues. --- **Organisms:** -Staph. aureus 30.0% -Coagulase-negative staphylococci 13.7% -Enterococcus spp. 11.2% -Escherichia coli 9.6% --- **Prevention:** Appropriate prophylactic Antibiotics 30-45mins before incision. Nasal screening and decolonization. Good glycemic control Normothermia
	Central line-Associated BloodStream Infection (CLABSI)	Laboratory-confirmed bloodstream infection by a positive blood culture that is not related to another site and develops 48h after central line placement. Most commonly from femoral central line --- **Organisms:** - Gram positive cocci 60% - Gram negative bacilli 16% - Candida spp. 12% - Other 10% --- **Prevention:** Hand Hygiene before wearing gloves. Strict aseptic technique including a full-body drape. Ultrasound guidance. Avoid femoral vein, prefer the subclavian. Use a checklist. Disinfect before accessing line. Replace administration sets every 96h except for lipid and blood sets. --- **Treatment:** Central line removal Antimicrobial therapy e.g. vancomycin, cefazolin, tazobactam...
	Ventilator-Associated Pneumonia (VAP)	One of the most common infections in intensive care units. **Pathogenesis:** Aspiration of secretions. Colonization of the aerodigestive tract. Use of contaminated equipment. **Prevention:** 1- Prevent aspiration of secretions 2- Reduce duration of ventilation 3- Reduce colonization of airway and digestive tract 4- Prevent exposure to contaminated equipment

4. Malaria & associated infections:

- Protozoa infection caused by a few plasmodium species that spreads by a mosquito. once it enters the bloodstream, it infects and destroys mainly liver cells and RBCs and causes various symptoms
- **Children under 5 are the most vulnerable group affected by malaria**
- Mosquitos **can't live in extreme temperatures** like cold and heat.
- People living in endemic areas have some kind of immunity against it (not permanent)
- Etiology: plasmodium
    - Spread to humans through **Female anopheles**
    - 5 different types cause malaria:
        - **Falciparum:**
            - Africa
            - **Most common**
            - Responsible for **most deaths worldwide**
            - **Treat always as if caused by fal because it's the most serious**
        - **Vivax:**
            - Asia and south America
            - **Milder disease but stays in the liver for up to 3 years > relapses**
        - **Ovale:**
            - West Africa
            - **Remain in liver for years**
            - Without producing symptoms
        - Malariae: Only in Africa
        - Knowlesi: southeast Asia
- Lifecycle:
    1. **Transmission from mosquito:** **Sporozoites** reach the liver within 1-2 hours following Female Anopheles mosquito bite.
    2. **Incubation period:** Pt. asymptomatic for 12-35 days until RBCs stage of parasite life cycle.
       Vivax & Ovale can develop what's called **HYPNOZOITES** which can stay **dormant** (sleeping) in the liver & result in reinfection up to years after the parasites have been cleared from blood.
        - P. Falciparum and malariae don't have exoerythrocytic
    3. **Symptomatic erythrocytic period:**
        - **Hepatic schizonts** burst> **Merozoites** > **into RBCs** (ring)
            1. **> trophozoites** > multiply > **RBC Schizont** ruptures and spreads **trophozoites** in bloodstream
            2. **> Gametocytes** > picked up by **female anopheles** > **Sporozoites** > infect someone else

- Pathogenesis
    - **RBCs invasion:**
        - Fal: **all ages of RBC**, Mal: **old**, Ovale and vivax: **young**

- **Microvascular pathology**
  - Secondary to adherence of non deformable parasitized (become rigid) RBC to endothelium > **occlusion of blood vessels**
- **Renal failure**: hemolysis and ischemia
- **Deep coma: hypoglycemia** and microvascular adherent parasitized RBC
- **Pulmonary edema:** secondary to capillary leak syndrome
- Immune complex nephrotic syndrome: secondary to mal species only

- Clinical features:
  - Vary with geography, epidemiology, and age
  - High risk groups: children, pregnant women, non immune travelers to malaria endemic areas
  - **Major clinical features:**
    - **Recurring fever**
    - **Chills associated with RBC lysis**
  - **Severe Acute: Falciparum infection** (>10 parasites/mcl)
    - **Renal failure**
    - **Coma** secondary to **hypoglycemia**, TNF, or microvascular pathology
    - **Pulmonary edema**
    - **Thrombocytopenia**
    - **Gastroenteritis > Diarrhea**
  - **Chronic:** P. Falciparum is usually acute but can be chronic when the mature parasite stays in the spleen causing splenomegaly.
    - **Splenomegaly**: mature parasite stays in spleen
      - Resolves after treatment with anti-malarials (6-12 months)
    - **Mal > immune complex nephrotic syndrome**
    - **Vivax > late splenic rupture with trauma** (1-3 months after infection)

- **Proxyms (attacks) Three stages:**
  1. **Cold**
     - Rigors
     - Headache
     - **Pale cold skin**
     - 1-2 hours
  2. **Hot:**
     - delirium
     - tachypnea
     - **hot skin**
     - several hours
  3. **Sweating:**
     - **fever**
     - sweating
     - fatigue (patient goes to sleep)
- Proxyms associated with **synchrony of merozoite release**
- **Between paroxysms temp is normal and patient feels well and asymptomatic**
- P.fal may not exhibit typical cycles
- **periodicity of attacks:**

    - **every 48 hours: vivax and ovale (tertian)**
    - **every 72 hours: malariae (quartan)**
    - **irregular: falciparum**
- Diagnosis:
    1. **detailed history** including travel and **clinical examination** with high index of suspicion **(HIS)**
    2. **blood film**
    3. Serology (not useful in acute patients)
    4. DNA probe (PCR): similar thick film sensitivity
- Acutely ill patients ddx is fal or vivax: Present acutely, morphologically and clinically the same.
- Mal: present chronically.
- **Blood film:** by **Giemsa stain or wright's stain**
    - **Correct identification** of species for treatment
        - Fal is resistant to chloroquine and others
    - Giemsa: cytoplasm > light blue nucleus > dark blue
    - **Fal: only ring stage**, asexual parasite, and gametocytes seen in peripheral blood
        - RBC with schizonts stage: sequestered in peripheral microvasculature, and not circulating in peripheral blood
    - **All asexual erythrocytic stages of vivax, ovale, and malariae circulate in peripheral blood > seen on smear**
- Thin vs thick film
    1. **Thin: morphology (RBC) is preserved**
        - In vivax infected RBC enlarge with parasite maturation
        - **Schuffner's dots** (eosinophilic dots in RBC cytoplasm)
        - May see **Mauere's clots in RBC cytoplasm**
    2. **Thick: RBC lysed**
        - You may examine 10 times more blood than in thin film
        - **More diagnostic in lower degree of parasitemia**
- **Ddx of malaria in acutely ill patient** based on peripheral blood smear:
    - **Fal: multiple infected, no enlargement of RBCs, and no mature parasites**
    - **Vivax and ovale: mature trophozoites and RBC enlargement**
- Mature (trophozoites & schizont) stage P. falciparum typically sequestered in the peripheral microvasculature.
- RBC enlargement in P. vivax typically occurs with later stage parasites.

- **Complications:** Majority associated with falciparum
    - **Anemia:**
        - **Parallels parasitaemia** and due to:
            - **Hemolysis of infected RBC**
            - Delayed reticulocyte release from bone marrow
            - Immune mediated hemolysis of non infected RBCs
            - **In non immune patients (primary):**
                - **Black water fever (hemoglobinuria)** and exaggerated haemolytic response to quinine sensitized RBCs
            - **Jaundice:**

        - Mild unconjugated is common and parallels **hemolysis**
        - **Hepatocellular dysfunction** may contribute to jaundice
    - **Tissue hypoxia:**
        - Due to **anemia + altered microcirculation**
    - **Falciparum:** parasitized **RBC sequestered in microcirculation** due to:
        - **Altered deformability of parasitized RBCs**
        - **Adhesion** involving parasite derived **proteins within RBC** and glycoproteins **on vascular endothelium**
- **Early** complications:
    - **Cerebral malaria:**
        - most severe common complication **caused by P.Fal**
        - **Risk factors for poor prognosis:**
            - **increased Creatinine** (nephropathy)
            - **increased bilirubin** (hepatic dysfunction)
            - **increased lactate**
        - Factors that **do not modify outcome** in cerebral malaria:
            - Depth of coma
            - Temp, vomiting, and seizures
            - Parasite load
            - Anemia, HIV
    - **Renal failure:**
        - Acute tubular necrosis
        - Dehydration
        - Hypotension
        - Hyperviscosity
    - **Pulmonary edema**
        - Acute respiratory distress syndrome and fluid overload contribute
    - **Hypoglycemia:**
        - Due to:
            - Glucose consumption (host and plasmodium)
            - Lactic acidosis
            - Quinine/quinidine increase **insulin secretion**
    - **Bleeding: thrombocytopenia** and consumption coagulopathy
    - Other: shock (endotoxemia), **diarrhea**, and **hyponatremia (SIADH)**
- **Late** complications:
    - **Tropical splenomegaly (repeated attacks)in** P.fal endemic areas
    - Nephrotic syndrome (malariae)
    - Burkitt's lymphoma due to (EBV or P.Fal)
- Hemoglobinopathies:
    - Malaria is **serious is all types of hemoglobinopathies**
    - Hetero sickle cell trait: children are less likely to contract fal
    - Hemoglobin S-C disease: no protection, **higher mortality**
    - Thalassemia: partial protection (fetal hb)
    - **G6PD: less prone to P.fal**
- **Pregnancy: always treat as Inpatient**

- Mortality
- Anemia, hypoglycemia, pulmonary edema
- Abortion and stillbirth
- High premature delivery, low birth weight, and placental insufficiency
  - **Placenta is a favorable site for P.fal**

- **Congenital** Malaria:
  - Transplacental infection
    - All 4 species
    - **Vivax and fal in endemic areas, Malariea in non endemic areas**
  - Neonate can be **diagnosed** with parasitemia within **7 days after birth** (if no other risk factors)
  - Fever, irritability, feeding problems, **hepatosplenomegaly, and jaundice**
  - Keep in mind even if mother has not been in malarious area for years before delivery.

Treatment:

- Principles:
  - The infecting Plasmodium species.
  - The clinical status of the patient.
  - The drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired and the previous use of antimalarial medicines.
- If species unknown treat as fal and **assume its chloroquine resistant** (except in central America and ME)
- **If vivax or ovale > primaquine**
- Uncomplicated: meaning creatinine, bilirubin and lactate levels are normal > no end organ damage
  - **P. Falciparum infection:**
    - **Artemether-Lumefantrine AKA Artesunate**
    - **Atovaquone-proguanil**
    - **Quinine**
      - If Artemether is not available, Quinine can be used but it causes cardiotoxicity and insulin secretion.
    - **Mefloquine**
  - Mal, vivax, ovale, fal **(sensitive)**:
    - **Chloroquine phosphate**
    - **Hydroxychloroquine**
  - Vivax (chloroquine):
    - Quinine, Atovaquone-proguanil, Mefloquine, Amodiaquine
- **Complicated:**
  - **Quinidine gluconate**
  - Once **parasitemia is < 1%**, and patient cant take oral medication > **quinine + doxycycline to prevent relapse**
    - **Pregnant: clindamycin instead of doxycycline**

- **Chemoprophylaxis:**

- Atovaquone-proguanil
- Chloroquine phosphate
- Doxycycline
- **Mefloquine,** safe for pregnant women.
- Primaquine 4 weeks before traveling, continue there and 1 week after.

5. Use of Antibiotics:

Obtaining an accurate infectious disease diagnosis

- **Determine the infection** (through symptoms)
- **Define the host** (immunity status: compromised or competent)
- **Establish a microbiological diagnosis**: endocarditis, septic arthritis, meningitis
    - **Exclude non infectious causes of fever**
        - § Adult onset still disease, drug induced, PE, lymphoma
    - **Bacterial or fungal** through culture and serology
    - **most likely etiological agent could be inferred from clinical presentation**
        - § cellulitis > strep or staph so just make sure your Abx covers both
- is an Abx indicated?
    - Clinical diagnosis of bacterial infection
        - § Ex. CAP > CXR shows consolidation >**treat empirically with macrolides or fluoroquinolone**
- Timing:
    - **Urgent**: empirically and immediately (with collection of diagnostic samples)
        - § **Acute meningitis**
        - § **Septic shock**
        - § **Febrile neutropenia**
    - **Non urgent:**
        - § **Febrile and stable w/ fever for several days**
        - § **Hold Abx until specimens have been collected and submitted**
        - § Ex. Subacute bacterial endocarditis
- Possible problems from a sputum sample:
    - False –ve
    - Normal flora
    - Can't give a definitive diagnosis

Empiric and definitive therapy

- Micro results do not become available before 24-72 hours
- **Empiric therapy guided by clinical presentation**
    - **Broad spectrum**
- **Inadequate therapy for** infections in the critically ill (hospitalized) > **greater morbidity and mortality**
- Which organism: Hx and PE > clue of Dx
    - Epidemiology: **hospital acquired or community acquired**

§ **Prior antibiotic use?**

- **Dyspnea + cough > strep pneumonia and atypical organism**
    - Prior Abx could kill the colonizers > make pneumonia difficult to treat
- **Fever + urinary symptoms > UTI: E Coli**
    - E Coli is exposed to too many Abx > resistant
- **Erythema over leg + pain + tenderness > GAS and staph**
- Hospital acquired:
    - **Catheter or central line associated bacteremia:**
        - § **Coagulase –ve staph**
        - § **MRSA**
    - **Catheter related UTI**
        - § **Gram –ve > pseudomonas**

Identifying opportunities to switch to narrow spectrum

- Once you know the pathogen and its susceptibility > narrow your Abx spectrum
    - Reduces cost and toxicity
    - Prevent resistance from emerging in the community
- Susceptibility testing:
    - The ability of an organism to grow in the presence of a drug in vitro
- MIC: the lowest concentration of an antibiotic that inhibits visible growth of organism
- Data is reported in the form of MIC:
    - Abx dose should exceed the MIC > kill organism
    - MIC 0.5: vancomycin
    - MIC > 2: vancomycin + another antibiotic
- Susceptible: isolate is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the recommended dosage is used.

Bactericidal vs Bacteriostatic

Bactericidal	Bacteriostatic
-Death and disruption of bacterial cell wall -Act on: 1. Cell wall: beta lactams 2. Cell membrane: daptomycin 3. Bacterial DNA: fluoroquinolones -Preferred in the case of serious infection like endocarditis, pneumonia, and meningitis > rapid cure	-Inhibits bacterial replication -Doesn't kill the organism -Act by inhibiting protein synthesis: 1. Sulfonamide 2. Tetracycline 3. Macrolides

Combinations:

- Why: synergy

- When: serious infection
  - **Rapid killing is essential**
    - **Endocarditis by enterococcus: penicillin and gentamicin > bactericidal**
  - **Shorten the course**
    - **Endocarditis by viridans: penicillin /ceftriaxone + gentamicin for 2 weeks**
      - Rather than just 1 for 4 weeks
  - **Polymicrobial infection**
    - **3rd gen cephalosporin/ fluoroquinolones + metronidazole**

Cost effective oral agents for the shortest duration needed

- mild – mod infections
- well absorbed oral antimicrobials
  - **Pyelonephritis > fluoroquinolones**
  - **CAP > augmentin and macrolide coverage**
- Bioavailability

Understanding drug pharmacodynamics and efficacy at site of infection

- Efficacy depends on capacity to achieve concentration equal or greater than MIC at site of infection
- SCF, ocular fluid, abscess cavity, prostate, and bone are lower than serum levels
- **1st and 2nd gen cephalosporins > don't cross BBB**
  - not used in meningitis
- **aminoglycosides > less active in low O2 states and low pH type of abscess**
- **fluoroquinolones > achieve high conc in prostate**
  - preferred oral agents in prostatitis
- **moxifloxacin > no significant urinary conc**
  - not suitable for UTIs
  - UTI > ciprofloxacin or fluoroquinolones

Host characteristics that influence antimicrobial activity

- Factors to be considered:
  - **Renal and hepatic function**
    - Delayed clearance > accumulation > toxicity
    - Nephrotoxic drug > further damage to the kidney and liver
  - **Pregnancy and lactation**
    - **Sulphonamide: kernicterus especially in preterm infants**
      - Cross BBB > severe damage
    - **Tetracycline > staining of teeth**
    - **Fluoroquinolones > cartilage damage**
    - **Thalidomide > phocomelia**
      - Biggest man made medical disaster
      - **Used for morning sickness and emesis in pregnant women**

    - **History of allergy or intolerance like penicillin**
    - **G6PD def, renal function, and liver function**
    - **Drug interaction**
- Assessing response to treatment
    - Clinical improvement
    - Lab: decreased leukocyte count
    - Radio: decrease size of abscess
- Prophylaxis:
    - **Presurgical: reduce incidence of SSI**
        - **Single dose of cephalosporin within 1 hour before incision**
    - **Before dental procedure**
        - Prosthetic valve or RHD > prevent endocarditis
    - **Prevent transmission of communicable disease**
        - **Ciprofloxacin > N meningitis (close contact)**
- Treating +ve culture with absence of disease:
    - Old women w/ indwelling catheters
    - Endotracheal tubes in mechanically ventilated patients
    - Chronic wounds
- **Dose:**
    - Lowest effective dose
    - Avoid sub-therapeutic dose
    - **Determined by:**
        - § **Serious infection?**
        - § **Site**
        - § **Drug properties**
        - § **Host factors**
    - **Modification principle:**
        - § **Narrow vs. broad**
        - § **least toxic agent**
        - § **cheaper**
- criteria for use of new agent:
    - Antimicrobial activity is superior.
    - Have a therapeutic advantage
    - Better pharmacokinetics:
        - § Site penetration
        - § Longer t 1⁄2
        - § Shorter duration
    - Less toxic.
    - Better tolerance.
- Four moments of Abx decision making:
    - Does the infection require Abx?
    - Have I ordered appropriate cultures? What empiric therapy should I start?
    - After a day or more: can I stop Abx? narrow down the therapy? Change from oral to IV?
    - What's the duration needed?
- **Appropriate use of antimicrobial agents involves:**

- **Accurate diagnosis**
- **Determine the need for and timing**
- **Dosing effects of different agents**
- **Tailoring treatment to host characteristics**
- **Narrowest spectrum + shortest duration + oral ASAP**
- **Non antimicrobial related interventions should be perused diligently**
  - § Like abscess drainage

Herpes viral infection:

- Microbiology:
  - DNA encapsulated virus
  - Latency after initial infection
  - Humans are the only reservoir
  - **Structure: 4 layers**
    - Double stranded DNA genome
    - Enclosed by an icosapentahedral capsid made of capsomers
    - Capsid surrounded by amorphous protein coat called tegument
    - Glycoprotein bearing lipid bilayer envelope
  - Replication:
    - Upon entry into the host cells 3 distinct phases of gene transcription and protein synyhesis > immediate-early, early, and late proteins
    - Viral nucleocapsid assembly occurs within host cells nucleus
    - Final envelope > budding into cytoplasmic vesicles
- Types:
  - **HSV-1:**
    - **Non genital**
    - Transmission: close direct contact
      - **Oral sex**
    - Cause of encephalitis
    - Latent infection stays in **trigeminal nerve**
    - **Primary**infection: **asymptomatic**but when symptomatic causes
      - **Systemic manifestations**like fever, sore throat, cervical lymphadenopathy
      - **Oral lesions**: blisters, painful
      - **Pharyngitis and gingivostomatitis (1st episode)**
    - **Recurrent: herpes labialis (cold sores)**
      - **Burning pain > blister or sore**
  - **HSV-2:**
    - **Genital and neonatal infection**
      - Intrauterine growth retardation, chorioaminionitis, and death
    - Transmission: close direct contact > **Sexual contact**

- Latent infection stays in **sacral root**
- **Primary: very painful genital vesicles**
    - Tender inguinal lymphadenopathy
    - Vaginal/urethral discharge
    - Itching and dysuria
    - Myalgias
    - Constitutional symptoms
- **Recurrent: no systemic symptoms (less severe, often painless)**

- Pathophysiology:
    - Exposure at mucosal surface or abraded skin site > entry of virus > initiation of its replication in epidermis and dermis
    - **After initial infection > sensory and autonomic nerves and become dormant in the ganglia (latent infection)**
- **Whitlow:**lesion on finger
    - HC workers like **dentists**
- Diagnosis: clinically mainly
    - **Serology: direct fluorescent assay and ELISA**
        - IgM: 1-2 weeks of infection
        - IgG: 3-4 weeks of infection
    - Viral culture (not used)
    - Cytology
    - PCR of CSF
- Treatment: as soon as prodrome symptoms appear before lesions appear
    - **First line: acyclovir**
    - Famciclovir, valacyclovir
    - Topical in mild cases:
        - Penciclovir or acyclovir
- **Herpes encephalitis:**
    - **HSV 1** is the most common cause of sporadic encephalitis
    - Risk factor: use of natalizumab
    - Survival and recovery are related to mental status at the time of therapy
        - Early diagnosis and treatment are important
    - Dx:
        - Commonly affects the temporal lobe
        - **PCR of CSF for HSV-1 DNA**
            - 25% of samples drawn before day 3 are negative, so if –ve and you're suspicious repeat in 3 days
            - -ve PCR is associated with low protein and <10 WBC
                - **examine mucosa > active sore > herpes encephalitis**
    - **treatment: IV acyclovir for 21 days (prolonged therapy)**

VZV

- **primary: chickenpox recurrent: shingles**
- **transmission: respiratory route and contact**
- replicates in nasopharynx or upper respiratory tract
    - Followed by localized replication at an undefined site, which leads to seeding of the reticuloendothelial system and, ultimately, viremia.

- **establishes latency within the dorsal root ganglia**
- Chickenpox IP: 10-21 days
- **Clinical features:**
    - **Disease of childhood <13 years**
    - **Fever, headache, malaise**
    - **Itching and blister like vesicular rash**
        - Chest, back, face > entire body
- Complications (in adults mainly):
    - Pneumonia, encephalitis, bacterial skin and soft tissue infections
- **Shingles:**
    - **Single or multiple dermatomes**
    - Disseminated organ involvement in immunocompromised
    - Unilateral distribution > single stripe that wraps around the left or right side of your trunk
    - **Facial: Ramsay hunt syndrome**
        - **Painful rash on the outer ear, LMN paralysis of facial nerve, loss of taste in ant 2/3 of the tongue**
        - Refer to optha and ENT > blindness and deafness
- Investigations:
    - **Serology: IgM > chickenpox IgG > shingles**
    - Viral culture (not used) and PCR
- Treatment: **acyclovir**
    - Valacyclovir, famciclovir
    - Immunocompromised: acyclovir IV for 7 days
- Prevention:
    - **Vaccine at min age of 1 (2 doses)**
        - Children and susceptible adults
    - **VZIG in susceptible persons at greater risk for complications ASAP after exposure < 96 hours**, if varicella develops start treatment <24 hours
    - **In hospital: isolation and contact precautions**
        - HCW who have Hx of chickenpox or Ab IgG +ve > don't need PPE

CMV

- **Largest virus that infects human beings**
- Clinical features:
    - **Primary: asymptomatic or infectious mono**
        - Fever, sore throat, lymphadenopathy
    - **Secondary: immunocompromised** esp. solid organs and stem cell transplant
- In transplant patients:
    - Now considered late onset **and occurs after stopping prophylaxis**
    - **SOT: sero+ve donor and sero-ve recipient**
        - **Lymphocyte depleting antibody therapy**
    - **HCT: sero-ve donor and sero+ve recipient**
        - **Graft vs host disease**
        - **T cell depleted or cord blood transplants**
- **Clinical disease:**
    - Fever, leukopenia, and thrombocytopenia w/o end-organ disease

- Gastrointestinal disease (colitis, esophagitis, enteritis)
- Hepatitis (very high ALT and AST)
- Pneumonitis multi-lobar patch disease
- CNS disease (meningoencephalitis, myelitis)
- Retinitis (Common in AIDS pts)
- Multisystem (cystitis, nephritis, etc.)

- **Investigations: depends on lab confirmation**
  - **Serology:**
    - **Latent > IgG**
    - **Primary > IgM**
  - **PCR (most common)**
    - **Viral load before and after treatment**
  - Viral cultures: blood, urine, and tissue
    - Not specific
  - Pp65 antigen: less commonly used and not recommended in neutropenic patients
  - **Histopathology: gold standard to confirm end organ disease**
    - **Owl eye inclusions**
- **Treatment: Ganciclovir**
  - Valganciclovir,foscarnet, cidofovir (resistant for Ganciclovir)
  - **Continue until: PCR or antigen becomes undetectable or clinical evidence of disease has resolved (**2-3 weeks at least)

EBV

- **spreads through intimate contact with an asymptomatic shedder**
- causes asymptomatic infection mainly
- **carcinogenic > burkitt's lymphoma and nasopharyngeal carcinoma**
- **clinical features: infectious mono**
  - fever, sore throat, lymphadenopathy
- **investigations:**
  - **heterophile antibodies (weak antibodies) transient**
  - **diagnostic test: Paul–Bunnell or 'Monospot' test**
  - **hematologic findings:**
    - **>50% mononuclear cells**
    - **Lymphocytosis (>10% atypical lymphocytes)**
    - Neutropenia thrombocytopenia
    - EBV specific antibodies
- **Treatment:**
  - **Supportive,** Steroids in severe cases

6. Common KSA endemic infections:

	Typhoid (Enteric) fever	Brucellosis	Gastroenteritis	
			Intestinal Amebiasi	Giardiasis
Definition	It is an acute febrile disease, caused by **Salmonella typhi** and S. paratyphi A, B, C.	Systemic febrile illness **Zoonosis.** *B. melitensis* and *B. abortus* Incubation period: **1 – 4 weeks**.		
Transmission	**ingestion of contaminated food or drink.**	- Contact with infected fluids or meat. - Rarely transmitted between humans.	By cysts	colonise upper small intestine
Pathogenesis	Penetrate ileal mucosa → Reach mesenteric lymph nodes & multiply → Invade Bloodstream → Infect multiple organs → bacilli pass into bloodstream**.**	Enters the body To lymph nodes To bloodstream Reticuloendothelial System To Blood to Any organ.		
Clinical Manifestation	Intermittent fever, malaise, headache, abdominal pain, constipation/diarrhea, **Rose spots**, enlarged spleen or liver. Will stay latent in the gallbladder!	Often fits one of the three pattern: - Acute febrile illness resembling typhoid. - Fever & acute monoarthritis. - low grade fever, low back pain, hip pain.	Asymptomatic - acute dysentery - chronic amebiasis - Causes invasive colitis	- Mostly Asymptomatic - abdominal pain, flatulence. - May become chronic.
Investigations	Blood culture (1st week), Stool culture (later weeks), Bone marrow, WBC, ESR. Widal is not a good test	WBC, ESR, Blood culture, Serology (NO diagnostic level >1:320)	stool microscopy , serology	stool microscopy
Treatment	- Fluoroquinolones **(ciprofloxacin)** drugs of choice - 3rd generation cephalosporins, **(Ceftriaxone)** are effective as alternative	**Uncomplicated**: - Streptomycin + Doxycycline - Rifampicin + Doxycycline - TMP/SMX + Doxycycline **Complicated**: Usually 3 anti brucella drugs for > 3 months 'rifampin'	Metronidazole	
Notes	**Complications:** Pneumonia, meningitis, osteomyelitis. **Intestinal hemorrhage and perforation.** - A **vaccine** is available	About 10% of patients relapse after therapy **Types**: - Osteoarticular disease - Genitourinary disease - Neurobrucellosis - Abscess of liver/spleen/abdomen	**Complication**: Liver abscess	

	Viral haemorrhagic fevers		Leishmaniasis	MERS-CoV
	Dengue	Rift Valley		
Definition	Arbovirus, causes **dengue and dengue hemorrhagic fever.** single-stranded RNA	An acute, fever-causing viral disease affecting animals and humans. Caused by RVF virus	A **protozoal disease** caused by Leishmania parasite	
Transmission	Aedes aegypti Mosquito	Contact with animals or insect (mosquito) bites	The **sand fly**	from camels to humans
Clinical Manifestation	**Dengue Fever:** - Fever, Headache, Muscle and joint pain, Nausea/vomiting, Rash, **Hemorrhagic manifestations** **Danger Signs:** - Abdominal pain, Persistent vomiting, Abrupt change from fever to hypothermia, Restlessness or somnolence	**Haemorrhage, blindness, meningoencephalitis** (complications only in a minority)		
Treatment	Symptomatic treatment Hydration Avoid NSAIDS or Aspirin = bleeding! Platelet transfusion only if platelets <10-20	Symptomatic		- Supportive Treatment - No vaccine - Experimental Treatment
Notes	**Prevention**: - Elimination & destruction of mosquitos and larval habitat - Personal protection against mosquito	Vaccines for veterinary use.	**Types:** - Cutaneous leishmaniasis - Mucocutaneous - Visceral (Kala azar)	**Diagnosis**: rRT-PCR for respiratory secretions.