Medicine TEAM 437

MED437 KING SAUD UNIVERSITY

Tuberculosis

Objectives :

- Overview of Tuberculosis (TB) Epidemiology.
- Transmission and Pathogenesis of TB.
- Testing for TB Infection and Disease.
- Diagnosis of TB Disease.
- TB Infection Control.
- Treatment for Latent TB Infection.
- Treatment for TB Disease.

Team:

Team Leader: Al Hanouf Al Jaloud
Team Members:
AlJoharah AlShunaifi Hadeel Awartani Rotana Khateeb
Revised by: Aseel Badukhon

Resources :

Doctors Slides + Notes: Dr. Awadh Alanazy
Books: Davidson, Kumar, Step up.

Overview of Tuberculosis (TB) Infection Epidemiology:

Bacterial infection.

Caused by **Mycobacterium tuberculosis (also called tubercle bacillus).**

Damages a person's lungs or other parts of the body.

Fatal if not treated properly.

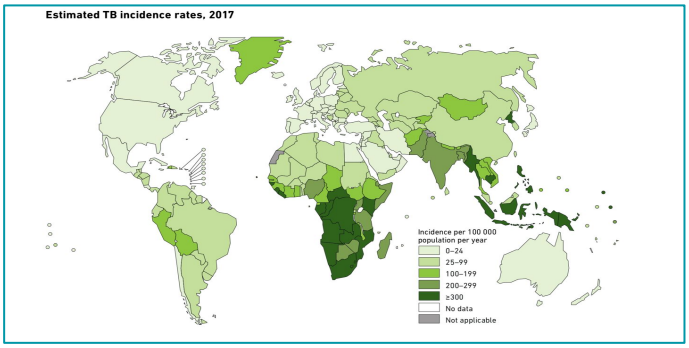
It is a world wide disease.

TB infects 1.7 billion with 3 million deaths/yr.

UK: 1st half of 20th century: a lot of death secondary to TB epidemic.

90% of cases and 95% of death occurred in developing countries.

Number of cases in developed countries has declined because of: case finding, RX and improved nutrition.



Microbiology:

Common problem in Diagnosis. There are other types of TB if pcr is (-) it means it not Mycobacterium TB but could be another TB

- **Mycobacterium tuberculosis.**
  - Aerobic. Could be in the middle lobe , depends on your immunity
  - Non-spore forming ,non-motile.
  - Rod: 2—5 mm long.
  - Resistant to disinfectant.
  - Once stained it resists decolorization with acid and alcohol facultative intracellular organism.
- Humans are the main reservoir of MTB.

Mode of spread and transmission

Inhalation of droplet nuclei spreads through the air when a person with active TB:

- Coughs/ Speaks/ Laughs/ Sneezes/ Sings. Microdroplets
- Another person breathes in the bacteria and becomes infected.

Tuberculous infection "Latent"**:**

A state in which the tubercle bacillus is established in the body without symptoms.

Tuberculous disease "Active"**:**

A state in which one or more organs of the body becomes diseased by the disease.

Only a small number of bacteria need to be inhaled for **infection** to develop but not all those who are infected develop **active disease**. The outcome of exposure is dictated by a number of factors "mentioned below"

What increases the spread of the disease:-

•crowding of living. "Prison inmates"

•migration of people from endemic area.

10% of infected people → active disease

50%of active disease → contagious

The risk of developing disease after TB infection :-

- Infecting dose.
- Host factors:
- Age: under 5 yrs.
- Debilitating illness and poor nutrition.
- Alcoholism.
- Gastrectomy.
- Diabetes mellitus.

Persons at higher risk for exposure to or infection with TB:-

- Close contacts to a person known or suspected to have active TB.
- Foreign-born persons from areas where TB is common.
- Persons who visit TB-prevalent countries.
- Residents and employees of high-risk congregate settings

People at higher risk of active TB disease:

•People with weak immune systems (especially those with HIV or AIDS).

•People with diabetes or silicosis.

•People infected within the last 2 years.

•People with chest x-rays that show previous TB disease.

•Illicit drug and alcohol abusers.

Pathogenesis :

Initial inhalation of droplet containing the bacilli to the alveoli. Bacilli proliferates subpleural.

Innate immune response activated

Macrophages ingest bacilli which continues to slowly proliferates inside..

Dendritic cells act as antigen presenting cell which leads to activation of adaptive response.

Cell mediated immunity is activated (T lymphocytes) wall off the affected macrophages forming a **granuloma (tubercles**: hard, grayish nodules with a center of caseous necrosis of dead cells). bacilli survive inside but cannot grow. Granulomas aggregate and form what is known as **Ghon's focus** "initial focus" which is usually presents subpleural and in lower lobes

Primary Active disease: Only in 5% of TB infection

Latent TB (LTBI): Granuloma persist, TB remain latent inside by host's immunity

Infection resolve: TB is lysised and granulomas undergoes fibrosis, sometimes calcification leaving scarred tissue.

Primary TB Takes **2-8 weeks**

Reactivation TB: when the host's immunity weakened and cannot contain the bacilli inside the granuloma. (ex: HIV, DM, Old age Immunosuppressants ..etc)
Usually in the **Apex of the lung** in the posterior segment

Post-Primary TB

- Pathogenesis can happen anywhere not only lungs
- A small number of tubercle bacilli can enter the bloodstream through lymphatic drainage and spread throughout the body.
    - The bacilli can reach any part of the body making **another focus**, including areas where TB disease is more likely to develop
    - such as the brain, larynx, lymph node, spine, bone, or kidney).
- TB require Cell Mediated Immunity for its control, AB response is rich but has no role.
- Multiplication proceeds for weeks both in initial focus and lymphohematogenous metastatic foci until development of cell mediated immunity.

Latent TB Infection (LTBI)

Anything that suppresses the immunity reactivates

- Granulomas may persist (LTBI), or may break down to produce TB disease.
- 2 to 8 weeks after infection, LTBI can be detected via TST or interferon-gamma release assay (IGRA). IGRA is Very expensive. Test the ones outside riyadh or old people who can't make it to the hospital regularly TST is cheap , do it to those who can make it to and don't have problems in coming back
- The immune system is usually able to stop the multiplication of bacilli. But they persist
- Persons with LTBI are not infectious and do not spread organisms to others.

TB Disease:

- In some, the granulomas break down, bacilli escape and multiply, resulting in TB disease.
- Can occur soon after infection (Primary Active TB), or years later (Post-primary reactivation). Adults most likely is due to reactivation from latency Children is primary infection
- Persons with TB disease are usually **infectious** and can spread bacteria to others
  - (laryngeal & open/smear +ve pulmonary TB).
- Positive *M.tb* culture confirms TB diagnosis.

Clinical features Active vs Latent

latent TB Asymptomatic (INFECTED) Not a TB case	Active TB Symptomatic (INFECTIOUS TB DISEASE)
Initial infection controlled by immune system.	Bacilli overwhelm immune system.
Bacilli remain **confined in tubercles** for years. (Inactive)	Bacilli **break out of tubercles** in alveoli and spread through bloodstream.
Usually **healthy person**	Usually **Unhealthy person**
Cannot spread TB bacteria to others	**May spread TB bacteria to others**
Asymptomatic.	**Symptomatic:** **Cough, fever, and/or weight loss might be present**
Positive TB skin test or TB blood test reaction.	**Positive TB skin test or TB blood test reaction indicating**
Radiograph is typically normal	**Radiograph may be abnormal**
Negative sputum smears and cultures	**Positive sputum smears and cultures**
Treatment for LTBI to prevent TB disease	**Treatment for TB disease**
Does not require respiratory isolation	**May require respiratory isolation**

Signs & Symptoms Not conclusive could be other symptoms

Pulmonary 80%.

The lung is usually the 1st organ involved in TB (middle common among diabetics and lower lobe) In severe cases primary lesion progress to clinical illness.

- cavitating pneumonia, lobar collapse due to lymph node enlargement.

- **Primary TB & LTBI:**
  - Usually Asymptomatic but might develop small pleural effusion, erythema nodosum
- **TB Disease (Active):**
  - Constitutional symptoms are common:
    - Fever, Night sweats, Chills
    - Loss of appetite, weight loss
  - Pulmonary symptoms:
    - As granulomas expand more lung tissue is destroyed, cavities develop in the lungs, which causes **coughing** and **shortness of breath**. Granulomas can also eat away blood vessels which causes bleeding in the lungs, and **bloody sputum.**
    - **Cough** is non-productive at first then productive, hemoptysis in more progressive disease
    - Pain while breathing, Fatigue, Swollen glands (lymph nodes).
    - Rales in chest exam.

Extra-pulmonary TB 20%:

- **Miliary TB:**
  - hematogenous dissemination of bacilli.
  - In 20% it affects the CNS
  - Systemic upset is the rule with respiratory symptoms
  - Liver and spleen microabscesses.
- lymphatic spread to any organ:
  - Lymph node, Pleural, Bone and joint, Meninges, Peritoneum.
- Symptoms of possible extrapulmonary TB:
  - Blood in the urine (TB of the kidney). one of the most common causes of **sterile** pyuria is kidney TB.
  - Headache/confusion (TB meningitis).
  - Back pain (TB of the spine).
  - Hoarseness (TB of the larynx).
- Constitutional symptoms are common as well.

Tuberculous lymphadenitis (25 %):

- The commonest
- Localized **firm non tender enlargement.**
- Common sites:
  - Cervical & Supraclavicular.
- Early: glands are discrete.
- Late: glands are matted -/+ sinus.
- Diagnosis:
  - FNA 30% in biopsy for histology and culture

Extra-pulmonary TB(Cont.)

Pleural Tb:

- Result form penetration by few bacilli into the pleural space resulting into pleural effusion and fever.
- Diagnosis;
  - aspirate, exudate.
  - AFB rarely seen
  - Culture 30% positive.
  - BX 80% granuloma

pleural biopsy (90%) + fluid especially in pleural effusion
If the the fluid is
(-) stain
(-) in culture
It DOESN'T RULE IT OUT

Skeletal TB :

- Source:
  - Reactivation of hematogenous focus.
  - spread from an adjacent LN.
- Common sites:
  - spine, hips and knees. Knee = aspirate the fluid, bone is very hard for biopsy

Spinal TB:

Cervical-> quadriplegia Low vertebrae -> paraplegia and urinary symptoms

- Dorsal site is the commonest site.
- Involve two vertebral bodies and destroy the disc in between.
- Advance disease .
  - Collapse fracture of the bodies causing kyphosis and gibbus deformity.
  - Paravertebral abscess(cold abscess).
- Diagnosis:
  - CT scan and MRI
  - Biopsy
    - Histopathology & AFB stain & culture. Biopsy to diagnose

Tuberculous meningitis: most major and serious TB

Unlike bacterial meningitis which is acute, TB is chronic with could be gradual onset and very rare.

Most often: children and may affect adults.

- **Source**:
  - Blood spread. could be miliary TB
  - Rupture of a subependymal tubercle.
- **Symptoms:**
  - Fever.
  - Headache.
  - Neck rigidity**.**
- Disease typically evolve in 2 wks
- **Diagnosis:** History and Lumbar puncture (lymphocytes and low glucose)
  - CSF studies:
    - AFB stain,WBC, culture, glucose, protein.

TB & AIDS

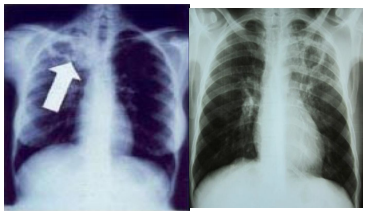
Each will make the other worse

- Person with active TB are more frequent to have HIV than general population.
- Almost 50% of TB cases are HIV +ve.
- Extrapulmonary is more common (40%).
- TB can appear at any stage of HIV infection but presentation varies with the stage.:
    - **Early:** They behave like any other person
        - Typical pattern of upper lobe infiltrate -/+cavitation. No granuloma due to low immunity
    - **Late:**
        - Diffuse infiltrate No cavitation Lymph Node enlargement.
- **Diagnosis is difficult:**
    - Sputum AFB is Negative in 40% of cases.
    - Negative TST (PPD).
    - Atypical CXR.

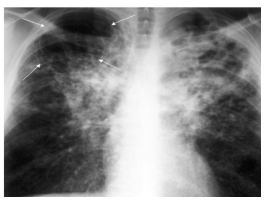
Diagnosis of TB

For any respiratory symptoms do chest X ray if abnormal collect sputum for culture & stain

- **1- Chest X ray:**
    - Classical findings:
        - Upper lobe infiltrates with cavitations.
    - Other possible findings:
        - Pleural effusion
        - Ghon complex and Ranke complex; evidence of healed primary TB
        - Atypical findings in Immunocompromised patients

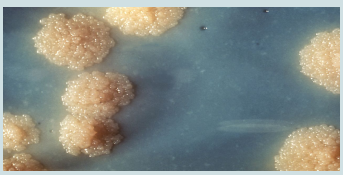


Big cavity

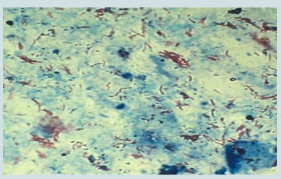


Diffuse infiltration

- **2- 3 morning sputum samples for:**
    - AFB Smear Ziehl-neelsen
    - Culture: Takes times If it's 3 days its atypical rapidly growing not TB
        - Solid media (lowenstein-jensen) or liquid (MGIT)
        - gold standard for confirming diagnosis of TB.
        - For definite diagnosis.
        - Culture all specimens, even if smear or NAA negative**.**
            - Results in 4–14 days when **liquid (**Bacticliquid **)** medium systems used.
            - Lowenstein-jensen media is slow, 3 - 6 weeks.
        - Culture monthly until conversion "2 consecutive negative cultures".



Colonies of M.tuberculosis growing on media

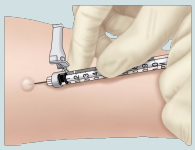


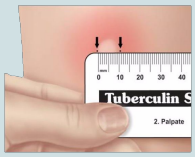
shown in red are tubercle bacilli in AFB smear

Diagnosis Cont.

- **3- Interferon gamma release assay (IGRAS)**
  - IGRAs detect *M.tb* infection by measuring immune response in blood.
  - Cannot differentiate between TB and LTBI; other tests needed.
  - May be used for surveillance/screening, or to find those who will benefit from treatment.
  - FDA-approved IGRAs are QFT Gold In-Tube and T-Spot.*T B* test.
  - May be used in place of, but not in addition to TST.
  - Preferred when testing persons who:
    - Might not return for TST reading.
    - Who have received BCG vaccination.
  - Generally **should not be used to test children <5 years of age, unless used in conjunction with TST.**

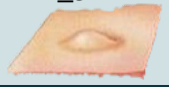
- **4- Tuberculin Skin Test (Mantoux Test)/(PPD)**





- 0.1 ml of **P**urified **p**rotein **d**erivative (5 tuberculin units), is injected between skin layers IN THE FOREARM using the Mantoux technique, Infected person's immune cells recognize TB proteins in PPD, respond to site, causing wheal to rise(Must follow universal precautions for infection control.).
- Takes 2-8 weeks after exposure and infection for the immune system to react to PPD.
- Reading and interpretation of TST reaction must be done **within 48–72 hours.**
- Diameter of induration across forearm is measured; **only measure induration, not redness.**
- Size of induration is recorded in millimeters; "0" if no induration found.

  - Limited value because of **low sensitivity and specificity**
  - Used for screening in high risk group for EXPOSURE to TB, such in Latent TB.
  - Not for active TB.

Test is positive if: Extra from book	
Induration:	In patients with:
≥15 mm 	• No risk factors
≥10 mm 	**High-risk populations** (e.g., those who live in high-prevalence areas, immigrants in the last 5 years, the homeless, prisoners, healthcare workers, nursing home residents, close contact of someone with TB, alcoholics, diabetics)
≥5 mm 	**HIV**, steroid users, organ transplant recipients, close contacts of those with ACTIVE TB, or those with radiographic evidence of primary TB

Diagnosis Cont.

Factors that may affect the skin test reaction

Type of Reaction	Possible Cause
False-positive	• Nontuberculous mycobacteria • BCG vaccination • Problems with TST administration
False-negative 20% of active disease	• Problems with TST administration or First time doing the test most common • Viral, bacterial, fungal coinfection • Recent TB infection • Very young age; advanced age • Live-virus vaccination • Overwhelming TB disease • Renal failure/disease • Lymphoid Lymphoproliferative disease,(lymphoma). • Malnutrition. Low protein states • Immunosuppressive drugs • Sarcoid

- **5- Nucleic Acid Amplification test for direct detection:**
  - Rapidly identify a specimen via DNA and RNA amplification.
  - Earlier lab confirmation of TB disease
  - Earlier respiratory isolation and treatment initiation
  - Improved patient outcomes; interruption of transmission
  - Perform at least 1 NAA test on each pulmonary TB suspect.
  - A single negative NAA test does not exclude TB.
  - Specific but not sensitive.
  - Can detect drug resistance

TB Infection Control measures

- TB infection control (IC) measures should be based on TB risk assessment for the setting. The goals of IC programs are:
  - Detect TB disease early and promptly.
  - Isolate persons with known/suspected TB.
  - Start treatment in persons with known/suspected TB.
- Active pulmonary tuberculosis: v.imp
  - Isolation of the patient (2wks). 1st thing to do
  - Isolation room should be negative pressure. Cause it is an airborne disease negative pressure prevents TB from getting out
  - Patient remain isolated until 3 negative smears and there is clinical improvement.

Treatment

Treatment goals:

- Cure patient, minimize risk of death/disability, prevent transmission to others.
- Provide safest, most effective therapy in shortest time.
- Prescribe multiple drugs to which the organisms are susceptible.
- Never treat with a single drug or add single drug to failing regimen.
- Ensure adherence and completion of therapy.

Current anti-TB drugs

10 or more drugs FDA-approved for treatment of TB:

- Isoniazid (INH). Give B6 supplements. 1st 2 months is very effective then gradually decreases
- Rifampin (RIF).
- Pyrazinamide (PZA).
- Ethambutol (EMB).
- Rifapentine (RPT).

- Streptomycin (SM).
- Cycloserine.
- Capreomycin.
- *P*- Aminosalicylic Acid.
- Ethionamide.

2nd line drugs:
More toxic, more Side effects,
Not as effective, Prolonged time

For all type of TB (miliary, pulmonary,...) the difference is just the duration:

- Pulmonary: 6 months
- Meningitis: 1 year
- Lymphadenitis 9 months

REGIMEN 1 FOR TREATMENT OF PULMONARY, DRUG-SUSCEPTIBLE TB

6-month standard regimen for most patients.

- Initial phase(First 2 months):
  - Isoniazid, Rifampin, Pyrazinamide, Ethambutol daily (7 or 5 days/week) for 8 weeks.
- 4-month continuation phase options:
  - Isoniazid, Rifampin daily (7 or 5 days/week) for 18 weeks.
  - Isoniazid, Rifampin intermittently (2 days/week or 1 day/week for Isoniazid, rifapentine) for 18 weeks
- Chemotherapy (the combination of the anti-TB drugs) is curative
- rapidly reduce the number of viable organism.
- kill the bacilli.
- slow rate of induction of drug resistance.

Drug Failure

- Non compliance. Most common.They think they are good so they stop
- Inappropriate drug.
- Drug resistance.

Treatment for latent TB infection(LTBI)

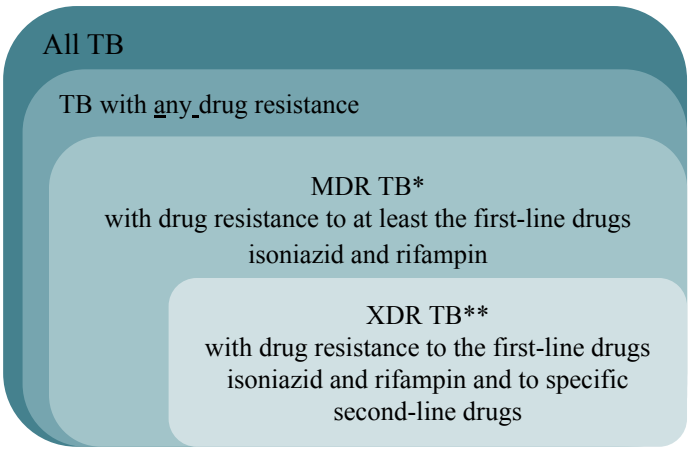
- Treatment of LTBI essential to controlling and eliminating TB disease.
- Reduces risk of LTBI to TB disease progression.
- Use targeted testing to find persons at high risk for TB who would benefit from LTBI treatment.
- Candidate for treatment of LTBI
    - **High-risk persons with positive IGRA test or TST reaction of ≥10 mm (cont.):**
    - **Persons with conditions that increase risk for TB:**
        - Silicosis.
        - Diabetes mellitus.
        - Chronic renal failure.
        - Certain cancers (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung).
        - Gastrectomy or jejunoileal bypass.
        - Weight loss of at least 10% below ideal body weight.
        - Children <4 years of age; children/adolescents exposed to adults in high-risk categories.
- 9 months of Isoniazid after active TB has been excluded

Drug resistant TB

- Caused by organisms resistant to one or more TB drugs
- Transmitted same way as drug-susceptible TB, and no more infectious.
- Delay in detecting drug resistance may prolong period of infectiousness because of delay in starting correct treatment.

MULTIDRUG-RESISTANT (MDR) AND EXTENSIVELY DRUG - RESISTANT (XDR) TB:

- Major nightmare. Very important is to never start empirically with the medications,
- MDR TB caused by bacteria resistant to best TB drugs, isoniazid and rifampin. Basic drugs is a big problem
- XDR TB caused by organisms resistant to isoniazid and rifampin, plus fluoroquinolones and ≥1 of the 3 injectable second-line drugs.



*Often resistant to additional drugs.
**Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

BCG vaccination

- Vaccine made from live, attenuated (weakened) strain of *M.bovis*.
- Early version first given to humans in 1921.
- Many TB-prevalent countries vaccinate infants to prevent severe TB disease.

BCG Contraindications

Contraindicated in persons with impaired immune response from:

- HIV infection, congenital immunodeficiency.
- Leukemia, lymphoma, generalized malignancy
- High-dose steroid therapy.
- Alkylating agents.
- Antimetabolites.
- Radiation therapy.
- **BCG vaccination should not be given to pregnant women**

Summary (436)

-Tuberculosis is a bacterial infection caused by **mycobacterium tuberculosis** (also called **tubercle bacillus**).
-**Transmission**: via airborne particles called **droplet nuclei (aerosoles).**
-Pathogenesis:
-Droplet nuclei → terminal air space →Multiplication → initial focus.
- Migration through blood and lymph node → another focus.
- Ingestion of the bacteria by the macrophage.

<table>
<tr><td rowspan="2">Signs and Symptoms</td><td>1-Pulmonary-TB</td><td>Symptoms: Fever, night sweat, Weight loss, Loss of appetite, Cough (non-productive <u>then</u> productive), haemoptysis, Fatigue, Swollen glands (lymph nodes), Chills, Pain while breathing.
Signs: rales in chest exam</td></tr>
<tr><td>2-Extrapulmonary-TB</td><td>Lymph node (Tuberculous lymphadenitis) , Pleural TB , Bone and joint (skeletal TB) , Meninges (Tuberculous meningitis) , peritoneum.</td></tr>
<tr><td>Diagnosis</td><td colspan="2">History, chest-x ray , bacteriology (AFB smear, culture), TST, IGRAs, NAAT</td></tr>
<tr><td>Risk Factors</td><td>People at higher risk of TB infection:
-Close contacts with people with infectious TB
-People born in areas where TB is common.
-Persons who visit TB-prevalent countries
-People with poor access to healthcare
-People who inject illicit drugs</td><td>People at higher risk of active TB disease:
-People with weak immune systems (especially those with HIV or AIDS)
-People with diabetes or silicosis
-People infected within the last 2 years
-People with chest x-rays that show previous TB disease (MDR-TB?)
-Illicit drug and alcohol abusers</td></tr>
<tr><td>Management</td><td>First line :
-Isoniazid (INH)
-Rifampin (RIF)
-Pyrazinamide (PZA)
-Ethambutol (EMB) -Rifapentine (RPT) -Streptomycin (SM)</td><td>Second line :
-Cycloserine
-Capreomycin
-ρ-Aminosalicylic acid
-Ethionamide</td></tr>
</table>

Questions

1. A 30--year--old man IV drug abuser came complaining of fever, night sweats and hemoptysis. AFB stain was positive. Also blood test revealed that he is positive to HIV with 50 cell CD4+. What is your next step in management?
A. Start antiretroviral then after that start TB medications.
B. Start antiretroviral till CD4+ become 350 cell then start anti TB.
C. Now treat only the HIV infection
D. Start anti TB medication at the same time with antiretroviral therapy

2. Which of following individual is at increased risk of mycobacterium tuberculosis infection?
A. A classmate of the patient with mycobacterium osteomyelitis.
B. Mother of a teenager with Mycobacterium meningitis.
C. Roommate of a patient with pulmonary tuberculosis.
D. A health care worker who interviewed a patient with pleural tuberculosis.

3. Which one of the following patient requires respiratory isolation?
A. 24 years old man admitted with weight loss, fever, oral & esophageal candidiasis, enlarged cervical node. Biopsy of which shows smear positive for acid fast bacilli.
B. 18 years old girl who was admitted with generalized lymphadenopathy, the FNA (fine needle aspiration) reveals histiocytic necrotizing lymphadenitis.
C. An aquarium sheep worker who present with hand discharging ulcer, biopsy of which shows mycobacterium marinum as culture.
D. 65 year old man with mediastinal lymphadenopathy

4.. Which of the following tests is the most important to follow for a patient receiving isoniazid and rifampin for tuberculosis treatment?
A. Renal function tests
B. Liver function tests
C. Slit-lamp examinations
D. Amylase and lipase tests

5. A 25-year-old woman is seen in the clinic because her father, who recently immigrated from South America, was diagnosed with and has been treated for tuberculosis. She denies a cough and her chest radiograph is normal. A PPD test shows 10 mm of induration. Her only medication is an oral contraceptive. Which of the following is the best next step?
A. Oral isoniazid and barrier contraception.
B. Combination therapy including isoniazid, rifampin, and pyrazinamide.
C. Observation.
D. Induce three sputum samples.

1-D 2-C 3-A 4-B
5-A : Because this woman is a household contact of a patient with active TB, she is among the highest risk group: her skin test would be considered positive with 5 mm induration. She has latent TB infection and should be offered treatment to prevent reactivation TB later in life. Oral contraceptives may reduce drug levels, so barrier contraception might be a better option for her.