433 Teams

MEDICINE

25 | Tuberculosis (TB)

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Objectives:

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

Overview of Tuberculosis (TB)

- **Bacterial** infection
- Damages a person's lungs or other parts of the body
- Fatal if **not** treated properly

Epidemiology:

- 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.
- No of cases in developed countries has declined because of: case finding & RX & Improved Nutrition
- Tuberculous **infection**: a state in which the tubercle bacillus is established in the body **without** symptoms.
- Tuberculous **disease**: a state in which one or more organs of the body becomes **diseased** by the disease.

What increases the spread of the disease?

1) Crowding of living 2) migration of people from endemic area.

- **10%** of infected people ---- **active disease**
- **50%** of active disease --- **contagious** (half of the 10% are contagious).

What increases the risk of developing disease after TB infection?

- Infecting dose
- Host factors
- Age: under 5 years
- Debilitating illness and poor nutrition
- Alcoholism
- Gastrectomy (due low HCL)

Microbiology:

- **Most commonly caused by Mycobacterium tuberculosis (MTB) and also called tubercle bacillus.**

- **Mycobacteria are acid-fast bacilli (AFB) considered slow-growing but hardy organisms. (Once stained it resists de-colorization with acid and alcohol facultative intracellular organism).**

- **Inhibited by the cellular arm of the immune system.**
- **Human is the main reservoir of MTB.**

Mode of Spread & Transmission:

- **M.TB spread via airborne particles called droplet nuclei.**
- **Expelled when person with infectious TB (active TB) coughs, sneezes, shouts, or sings**
- **Transmission occurs when droplet nuclei inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi.**

Risk factors (People at higher risk of active TB disease):

A. HIV-positive patients

B. Recent immigrants (within the past 5 years)

C. Prisoners

D. Health care workers

E. Close contacts of TB patient

F. Alcoholics

G. Diabetics

H. Glucocorticoid use

I. Hematologic malignancy

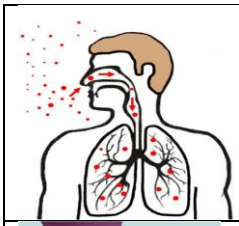
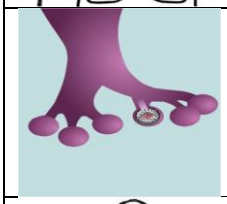
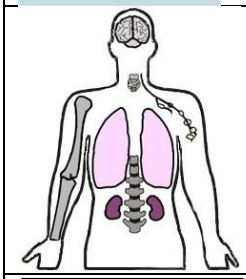
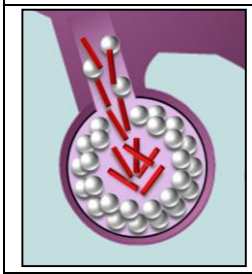
J. Injection drug users

K. People infected within the last 2 years

L. Close contacts of active TB patient

Pathogenesis:

- **Droplet nuclie ---terminal air space ---Multiplication … initial focus**
  - **Subpleural**
  - **75%single**
- **Migration through blood and lymph node --- another focus**
- **Ingestion of the bacteria by the macrophage --- slow multiplication**

	Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.
	Tubercle bacilli multiply in the alveoli.
	A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).
	Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (LTBI). (IMMUNO-COMPETENT HOST)
	If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone. (IMMUNO-COMPROMISED HOST)

Inside the Body:

- Breathe in infected air and bacilli go to lungs through bronchioles
- Bacilli infect alveoli
- Macrophages attack bacteria, but some survive
- Infected macrophages separate and form tubercles
- Dead cells form granulomas.
- As a person breathes in infected air, the bacilli go to the lungs through the bronchioles. At the end of the bronchioles are alveoli, which are balloon-like sacs where blood takes oxygen from inhaled air and releases carbon dioxide into the air exhaled.
- TB bacilli infect the alveoli and the body immune system begins to fight them. Macrophages — specialized white blood cells that ingest harmful

  Organisms — begin to surround and "wall off" the tuberculosis bacteria in the lungs, much like a scab forming over a wound.

- **Then, special immune system cells surround and separate the infected macrophages. The mass resulting from the separated infected macrophages are hard, greyish nodules called tubercles.**
- **Active TB spreads through the lymphatic system to other parts of the body. In these other parts, the immune system kills bacilli, but immune cells and local tissue die as well. The dead cells form masses called granulomas, where bacilli survive but don't grow.**
- **As more lung tissue is destroyed and granulomas expand, cavities develop in the lungs, which causes more coughing and shortness of breathe. Granulomas can also eat away blood vessels which causes bleeding in the lungs, and bloody sputum.**

Immunological Feature:

- **TB requires cell-mediated immunity (CMI) for its control.**
- **Antibodies response is rich but has no role**
- **Multiplication proceeds for weeks both in:**
  - **Initial focus**
  - **lymphohaematogenous metastatic foci**
- **Until development of ... cell mediated immunity**

Davidson Page.688:
- Mainly macrophages will undergo transformation into epitheliod and Langhans cells, Which aggregate with lymphocytes to form the classical tuberculous granuloma.
-Numerous granulomas aggregate to form a primary lesion (Ghon focus).Which is Characteristically situated at the periphery of the lung. Spread of the organisms to the hilar
Lymph nodes is followed by a similar pathological reaction. The combination of the primary
lesion and the regional lymph nodes in known as (The primary complex of Ranke).

- **Clinical Features Active VS. Latent Infection:**

➢ **Unhealthy person**
- **Bacilli overwhelm immune system**
- **Bacilli break out of tubercles in alveoli and spread through bloodstream**
- **This is (active) TB**

➢ **Healthy person**
- **Initial infection controlled by immune system**
- **Bacilli remain confined in tubercles for years**
- **Not contiguous**
- **This is (latent) TB**

If a surgeon is planning to send the organism for microbiology, then they should put it in SALINE instead of FORMALIN (Because formalin kills the organism = NO culture!)

- **Difference between active and latent TB:**

Person with Latent TB:	Person with active TB:
-Has no symptoms **-Does not feel sick** **-Cannot spread TB to others** **-Usually has a positive skin test** **-Has a normal chest x-ray and sputum test**	**-has symptoms (cough, fever, weight loss, night sweats, fatigue, loss of appetite, swollen glands(lymph node), chill, pain while breathing) ----may spread TB to others** **-has a positive skin test** **-May have an abnormal chest x-ray, or positive sputum smear**

Clinical Features:

- **Pulmonary 80%**
- **Extra pulmonary 20%**

Pulmonary tuberculosis:

- Primary: **the lung is the 1st organ involved … middle and lower lobe**
- Health: asymptomatic
- Heals spontaneously
- CXR normal

Post primary (reactivation):

- **Result from endogenous reactivation of latent infection and manifest clinically:**
- Fever and night sweat
- Weight loss
- Cough… non-productive then productive
- May have hemoptysis
- **Signs: Apical rales in chest exam**

Extra pulmonary :

1-Any organ:

- Lymph node (the commonest manifestation)
- Pleural
- Bone and joint
- Meninges
- Peritonium

2-Miliary TB*

Tuberculous lymphadenitis 25%

- The commonest **Localized painless swelling**
- Common sites: **cervical & supraclavicular**
- Early: glands are discrete
- Late: glands are matted -/+ sinus
- Dx: **FNA 30% in biopsy for histo and culture**

Pleural Tb:

- Result form penetration by few bacilli into the pleural space resulting into :
- **pleural effusion and fever**
- DX; aspirate --- exudate
- **AFB rarely seen**
- culture 30% positive
- **BX 80% granuloma**

Skeletal Tb :

- Source: **reactivation of haemato**
- **genous focus spread from an adjacent LN**
- Common sites: **spine- hips – knees.**
- Spinal Tb:
- **Dorsal site is the commonest site**
- Involve two vertebral bodies and destroy the disc in between.

Advance disease of skeletal TB:

- Collapse fracture of the bodies --
- **Kyphosis and gibbus deformity**
- **Paravertebral abscess(cold abcess)**
- Dx: CT scan and MRI
- Biopsy: histopath& AFB stain&culture

Tuberculous meningitis

- Most often: children and may affect adult
- Source: **Blood spread & Rupture of a sub-ependymal tubercle**
- Symptoms: **fever & headache & neck rigidity**
- Disease typically evolve in 2 wks.
- Dx: **CSF Studies:AFB stain, wbc,cult,glucose,protein…**

Note (from step up)* **Miliary TB refers to hematogenous dissemination of the tubercle bacilli, common in HIV patient , reticulonodular infiltrates on CXR, and choroidal tubercles in the eye.**

- Malnutrition
- HIV
- **Severe cases:**
- primary lesion progress to clinical illness
- cavitating pneumonia
- lymphatic spread and lobar collapse due to LN.
- 40% haematogenous dissemination

In children

- **Asymptomatic state may cause miliary tuberculosis and TB meningitis.**

TB & AIDS: HIV patients should be tested for TB (and vice versa)

- **Person with active TB are more frequent to have HIV than general population**
- **AIDS in HAITIANS: almost all children are positive for PPD --- active TB in 60%**
- **New York: 50% of active TB patients are HIV+**
- **Africans: 60% of active TB patients are HIV+**
- **TB can appear at any stage of HIV infection But presentation varies with the stage:**
- **Early: Typical pattern of upper lobe infiltrate -/+cavitation.**
- **Late: Diffuse infiltrate - no cavitation –Lymph Node.**
- Sputum is less frequent to be + for AFB with HIV than without Extra pulmonary is more common 40%
- Pulmonary TB and HIV diagnosis is difficult:
  - sputum (-) in 40 % – atypical CXR -- negative PPD

Latent TB Infection:

- 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)**
- The immune system is usually able to stop the multiplication of bacilli
- Persons with LTBI are not infectious and do not spread organisms to others
- In some, the granulomas break down, bacilli escape and multiply, resulting in TB disease
- Can occur soon after infection, or years later
- Persons with TB disease are usually infectious and can spread bacteria to others
- **Positive M. TB culture confirms TB diagnosis**

Person with LTBI (Infected)	Person with TB Disease(Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	**Has a large amount of active TB bacteria in his/her body**
Cannot spread TB bacteria to others	**May spread TB bacteria to others**
Does not feel sick, but may become sick if the bacteria become active in his/her body	**May feel sick and may have symptoms such as a cough, fever, and/or weight loss**
Usually has a TB skin test or TB blood test reaction indicating TB infection	**Usually has a TB skin test or TB blood test reaction indicating TB infection**
Radiograph is typically normal	**Radiograph may be abnormal**
Sputum smears and cultures are negative	**Sputum smears and cultures may be positive**
Should consider treatment for LTBI to prevent TB disease	**Needs treatment for TB disease**
Does not require respiratory isolation	**May require respiratory isolation**
Not a TB case	**A TB case**

Diagnosis:

- Medical history
- Symptoms of TB (**chough more than 3 weeks**, hemoptysis, **night sweat**, **weight** loss ,**fever**, loss of appetite)
- The **best initial test is a chest x-ray** as with all respiratory infections.
- **Sputum stains and culture specifically for acid-fast bacilli (mycobacteria)**
- **must be done 3 times to fully exclude TB.**
- **Pleural biopsy is the single most accurate diagnostic test.**

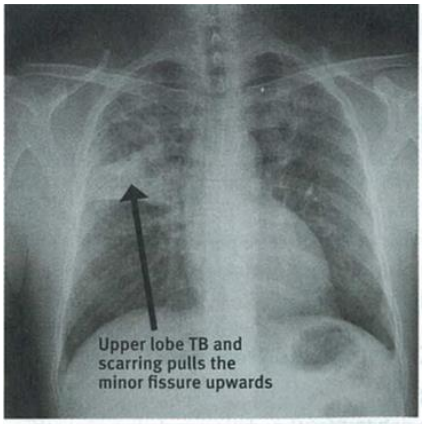
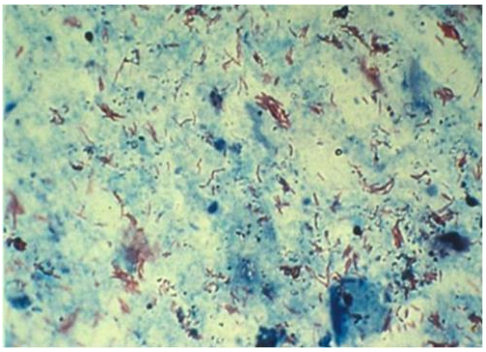
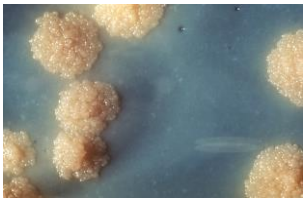


Figure 5.10: Chest x-ray with upper lobe disease consistent with tuberculosis. *Source: Craig Thurm, MD.*



AFB Smear
AFB (shown in red) are tubercle bacilli

Culture:



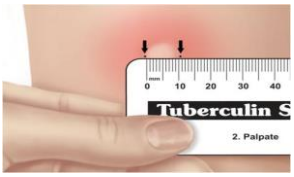
Colonies of *M. tuberculosis* Growing on Media

- Remains **gold standard for confirming diagnosis of TB**
- Culture all specimens, even if smear or NAA negative
- Results in 4–14 days when liquid medium systems used
- Culture monthly until conversion, i.e., 2 consecutive negative cultures

Latent Tuberculosis (PPD Testing):

•**Indications for PPD Testing (Mantoux Tuberculin Skin Test (TST)**
•The **Purified protein derivative (PPD)** is not a general screening test for the whole population. Only those in the **risk groups previously described should be screened. PPD testing is not useful in those who are symptomatic or those with abnormal chest x-rays.**
• **These patients should have sputum acid fast testing done.**
•**Everyone with a reactive PPD test should have a chest x-ray to exclude active disease.**

What Is Considered a Positive Test?



Only induration is counted towards a positive test. Erythema is irrelevant.

Induration larger than 5 millimeters:	Induration larger than 10 millimeters	Induration larger than 15 millimeters
• **HIV-positive patients** • **Glucocorticoid users** • **Close contacts of those with active TB** • **Abnormal calcifications on chest x-ray** • **Organ transplant recipients**	• Recent immigrants (past 5 years) • Prisoners • Healthcare workers • Close contacts of someone with TB • Hematologic malignancy, alcoholics, diabetes mellitus	Those with no risk factors

Two-Stage Testing:

If the patient has never had a PPD skin test before, a second test is indicated within 1 to 2 weeks if the first test is negative. This is because the first test may be falsely negative. If the second test is negative, it means the patient is truly negative. If the second test is positive, it means the first test was a false negative. Interferon gamma release assay (IGRA) is a blood test equal in significance to PPD to exclude TB exposure. There is no cross-reaction with BCG.

Interferon Gamma Release Assays (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**
- **General Recommendations for Using IGRAs:**

✓ **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 **shouldn't be used** to test <5 years of age, unless used in conjunction with TST

BCG Vaccination:

- Vaccine made from live, attenuated (weakened) strain of **M. bovis**
- Many TB-prevalent countries vaccinate infants to prevent severe TB disease.
- **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.**

Treatment of active TB:

When the smear is positive, begin therapy **with 4 drugs**:

Rifampin, Isoniazid, Pyrazinamide, and Ethambutol (RIPE). For first 2 months

You do not need the ethambutol if it is known at the beginning of therapy that the organism is sensitive to all TB medications. Ethambutol is given as part of 4-drug empiric therapy prior to knowing the sensitivity of the organism. After using RIPE for the first 2 months, stop ethambutol and pyrazinamide and **continue rifampin and isoniazid for the next 4 months. The standard of care is 6 months total of therapy.**

Indications to use Rifampicin in Brucella:

Brucella endocarditis ,Brucella neurology ,Brucella in pregnancy

Other than that, the use of **Rifampicin is limited to TB**.

Treatment is extended **to 6 months** for:

1-Osteomyelitis 2- Miliary tuberculosis 3- Meningitis

4- Pregnancy or any other time pyrazinamide is not used.

Use of Steroids:

Glucocorticoids decrease the risk of constrictive pericarditis in those with pericardia. They also decrease neurologic complication in TB meningitis.

Adverse effects of anti TB drugs

Drug	toxicity	management
Rifampin	Red color to body secretions	None, benign finding
Isoniazid	Peripheral neuropathy	Use pyridoxine to prevent
Pyrazinamide	Hyperuricemia	No treatment unless symptomatic
ethambutol	Optic neuritis, color vision	Decrease dose in renal failure

Note : **pregnant should not use pyrazinamide or streptomycin .**

Treatment for a Positive PPD or IGRA:

- After active tuberculosis has been excluded with a chest x-ray, **patients should receive 9 months of isoniazid.** A positive PPD confers a 10% lifetime risk of tuberculosis. **Isoniazid results in a 90% reduction in this risk**; after isoniazid, the lifetime risk of TB goes from 10% to 1%. **The PPD test should not be repeated once it is positive. Use pyridoxine (BG) with isoniazid**. Those at high risk, such as healthcare workers, should have a PPD done every year to screen for conversion. Most of the risk of developing active TB lies within the first 2 years after conversion.

  Note: When PPD is +ve , it will always be +ve in the future.

- **Infection Control:**
  - Active pulmonary tuberculosis:
    - ✓ **Isolation of the patient (2wks)**
    - ✓ **Isolation room should be negative pressure to keep the air in and prevent the spread of the disease.**
    - ✓ **Patient remain until 3 negative smears and there is Clinical improvement**
  - ✓ TB infection control (IC) measures should be based on TB Risk assessment for the setting.

MCQs

Q1/ A 22-year-old male patient, recently incarcerated and now homeless, has received 1 week of clarithromycin for low-grade fever and left upper-lobe pneumonia. He has not improved on antibiotics with persistent cough productive of purulent sputum and flecks of blood. Repeat chest x-ray suggests a small cavity in the left upper lobe. Which of the following statements is correct?

a. The patient has anaerobic infection and needs outpatient clindamycin therapy.
b. Sputum for acid fast bacilli stain and culture is required.
c. The patient requires glove and gown contact precautions.
d. Isoniazid to treat latent tuberculosis should be started if PPD is positive.
e. Interferon-gamma release assay should be ordered.

Q2/ A patient with a previous history of tuberculosis now complains of hemoptysis. Chest x-ray reveals an upper lobe mass with a cavity and a crescent-shaped air-fluid level.
With these clinical descriptions, what is the most likely etiologic agent ?

a. Aspergillus flavus
b. Coccidioides immitis
c. Herpes simplex type 1
d. Herpes simplex type 2
e. Hantavirus
f. Coxsackievirus B
g. Human parvovirus

Answer 1-B 2- A

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