# Tuberculosis

## Objectives :

By the end of this lecture, students should know the following about Tuberculosis:

- ★ Overview of Tuberculosis (TB) Epidemiology.
- ★ 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.

Editing file

**Color index**

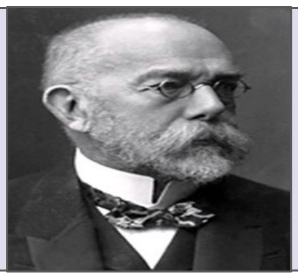
Original text
Females slides
Males slides
Doctor's notes [438]
Doctor's notes [439]
Text book
Important
Golden notes
Extra

# Introduction

## ◄ History of TB:

- TB has affected humans for millennia
- Historically known by a variety of names e.g:
  - Consumption
  - Wasting disease
  - White plague
- TB was a death sentence for many


- Scientific Discoveries in 1800s
  - Until mid-1800s, many believed TB was hereditary
  - 1865 Jean Antoine-Villemin proved TB was contagious
  - 1882 Robert Koch discovered M. tuberculosis the bacterium that causes TB



**Robert Koch**

The Nobel Prize in Physiology or Medicine 1905

- Koch discovered the tubercle bacillus in 1882
- He developed a staining and destaining method for acid-fast bacilli
- He also discovered a method of growing it in pure culture.
- He sought to cure TB by means of a preparation, which he called tuberculin,made from cultures of tubercle bacilli.
- The curative value of this was disappointing; but it led, nevertheless, to the discovery of substances of diagnostic value (tuberculin skin test).

- **Diagnostic tools that Koch used:**
  - Microscopy
  - Culture
  - Tuberculin test

# Overview of Tuberculosis



## ◄ Microbiology of Mycobacterium tuberculosis:

**Characteristics:**

- Facultative intracellular rod-shaped bacteria.
- Spreads via **aerosol droplet nuclei.**

**Culture mediums for growth**

- **Löwenstein Jensen medium.**
- Middlebrook medium.
- Rapid automated **broth culture.**

**Special stains[3]** (because it doesn't stain well with Gram Stain)**:**

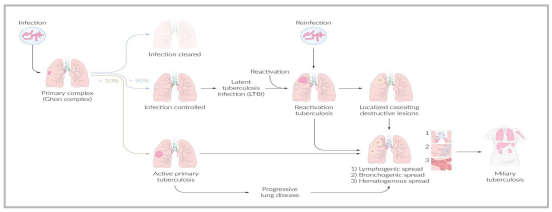
- **Ziehl-Neelsen stain**: acid-fast bacilli appear pink.
- **Auramine-rhodamine stain.**

**Mechanism of resistance**

- Remains viable in airborne droplet nuclei and soil.
- Able to survive in acidic conditions.

## ◄ Types of Tuberculosis[1]

❖ Not all those who are infected develop **active disease.**




| | Primary tuberculosis (primary infection)[2] | |
|---|---|---|
| | **Latent tuberculosis infection (LTBI)** | **Active primary tuberculosis** |
| **Definition** | • A state of constant immune response stimulation due to M. tuberculosis antigens, with **no signs of active TB**. | • Active TB disease occurring after first-time exposure to M. tuberculosis (only in 1–5% of cases). |
| **Features** | • **Asymptomatic**.<br>• **Not contagious.**<br>• The risk of reactivation is 5–10% during the course of a lifetime. | • **Symptomatic.**<br>• **Contagious.**<br>• Progressive primary tuberculosis is a severe form of disease seen in individuals with impaired immune systems (e.g., HIV, malnutrition) or immature immune systems (e.g., young children). |
| **Diagnostics** | • **Tuberculin skin test (TST)**<br>• **interferon-γ release assay (IGRA)** | • Bacteriological: **acid-fast staining, PCR, and culture.**<br>• Radiographic: chest x-ray. |
| **Treatment** | **Preferred regimens:**<br>• Isoniazid PLUS rifapentine weekly for 3 months.<br>• OR rifampin daily for 4 months.<br>• OR isoniazid PLUS rifampin daily for 3 months.<br>• Alternative regimen: isoniazid daily for 6 or 9 months. | • Intensive phase: rifampin PLUS isoniazid, pyrazinamide, and ethambutol for 2 months.<br>• Continuation phase: rifampin PLUS isoniazid for 4 months. |

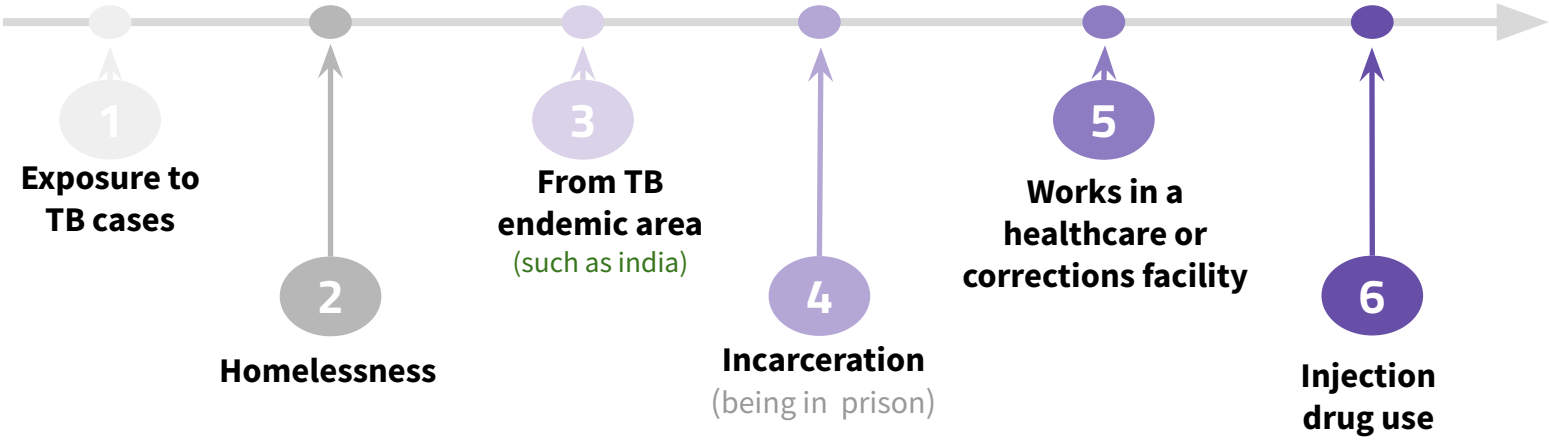
1- secondary infection is when there is **reactivation of TB or an exogenous reinfection.** the pt. will be symptomatic and contagious.
2- 'Primary TB' describes the **first infection with TB**. When the bacteria reach the alveolar macrophages, they are ingested and the subsequent inflammatory reaction results in tissue necrosis and formation of a **granuloma**. These granulomatous lesions consist of a central area of necrotic material called **caseation**, surrounded by epithelioid cells and Langhans giant cells.
3- Auramine–rhodamine staining is more sensitive (though less specific) than Ziehl–Neelsen; as a result, it is more widely used.

# Tuberculosis (TB)

## ◀ Overview of TB epidemiology

- After exposure to TB the patient will either present with an **active TB** or will just remain in a **dormant latent phase of TB.**
- Whether the patient had the infection or developed latent TB, **TST or IGRA will be positive.**
- The rate of progression from latent TB to active disease:
  - **Non-HIV** patients is 5-10% **lifetime.** (Especially in the first two years after developing latent TB)
  - **HIV positive** patients: 5-10% **per year.**

## ◀ Risk factors for TB infection




## ◀ Risk factors for progression to TB disease

| | | | |
|---|---|---|---|
|  | **Recent infection** (especially within first 2 years of exposure) **(The most important risk factor).** |  | Diabetes |
|  | **HIV infection** |  | Silicosis |
|  | TNF alpha inhibitors ( e.g. infliximab, rituximab). |  | CXR showing fibrotic lesions consistent with prior TB and granulomas |
|  | Immunosuppression |  | Intestinal bypass, gastrectomy or chronic malabsorption. (anything that causes malnourishment) |
|  | End stage renal disease |  | Cancer of the head or neck, **Hodgkin, leukemia.** |

## ◀ Transmission and pathogenesis of TB : Obj.

- M. tuberculosis is spread by the inhalation of **aerosolised droplet nuclei** from other infected patients.
- Once inhaled, the organisms lodge in the alveoli and initiate the recruitment of macrophages and lymphocytes.
- Macrophages undergo transformation into **epithelioid and Langhans cells**, which aggregate with the lymphocytes to form the classical tuberculous granuloma.
- Numerous granulomas aggregate to form a primary lesion or '**Ghon focus**' (a pale yellow, caseous nodule ) which is characteristically situated in the periphery of the lung.

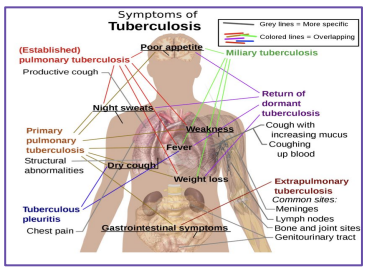
# Active TB Clinical presentation

## ◀ General symptoms

❖ Usually develop over **weeks or months** especially the malaise and weight loss with an average of 3-6 months .

**Fever** **Sweats** **Weight loss**

**Decreased appetite** **Malaise**

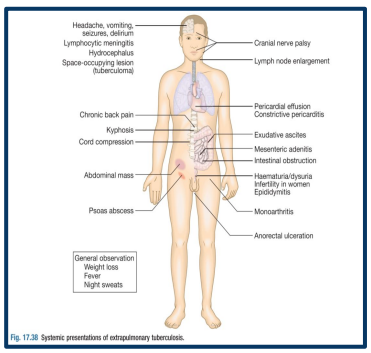



## ◀ Pulmonary TB

- **Cough with purulent sputum** that is occasionally blood-streaked **(hemoptysis)** in cases of cavitation (However, the **absence of hemoptysis should not exclude TB** as it usually develops if there was a cavitary lesion).
- Shortness of breath, Pleuritic chest pain.
- **Subacute in onset**
  - ★ **Can be acute in immunocompromised patients.**

## ◀ Extra-Pulmonary TB

- TB can virtually affect any organ and any system.
- It is reasonable to think about when patients do not respond to the typical therapy.
- It is important to obtain **clinical specimens from the site affected** for mycobacteriological cultures, PCR, smears and pathology.

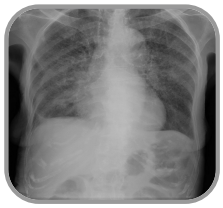



| CNS | ★ Lymphadenitis | Bone and joint |
|---|---|---|
| Meningitis(headaches, visual changes), focal tuberculomas, | **Cervical (most common)**, thoracic or abdominal lymph nodes | Vertebral (**Thoracic -most common-**, lumbar, anterior wedging ± psoas abscess). Osteomyelitis and arthritis. |

| Pleural | Abdomina (GI) | Pelvic (GU) |
|---|---|---|
| Pleuritis, chest pain | A great mimicker for **inflammatory bowel disease (it can cause pancolitis,** diarrhea & ascites) | **Sterile pyuria**, can cause infertility (men) |

## ◀ Disseminated (Miliary) TB

- Miliary TB is a **hematogenous** spread TB.
- **Clinical features:**
  - Can present with an acute sepsis-like syndrome, especially in heavily immunocompromised patients.
  - Mostly nonspecific, could include **lymphadenopathy** or **hepatosplenomegaly**.
- **Diagnosis**:
  - Obtain mycobacterial **blood cultures** and **respiratory specimens**.
  - **Chest x-ray:** multiple small nodules (< 2 mm) with an appearance resembling millet seeds.
  - **All patients should have brain imaging (MRI)**, to look for evidence of cerebral disease, which can present as an **asymptomatic brain tuberculoma.**


Miliary TB

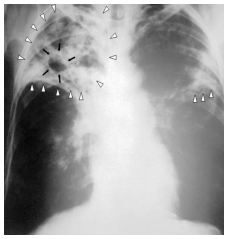
# Active TB Diagnosis



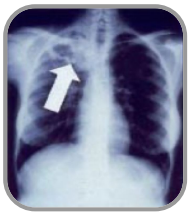
| | |
|---|---|
| **Smear microscopy (Ziehl-Neelsen stain "Acid fast bacilli")** | • **Sensitivity:**<br>  ○ Has a **low sensitivity overall** around 50-60% sensitivity in pulmonary TB (this is why In pulmonary TB the yield of test is increased with multiple specimens; **so we usually take at least for 3 different sputum sample that are 8 hours apart. one has to be first thing in the morning to increase the yield to 80-90% )**<br>  ○ Less sensitive in advanced HIV (30-50%).<br>• **Specificity**: **Not specific for MTB** (Most mycobacteria look alike).<br>• Good Positive Predictive Value (PPV) in **TB endemic regions.**<br>• Needs 10,000 cfu/ml. cfu=colony forming units<br>• A **negative smear does not exclude the diagnosis of active TB**. |
| **Rapid MTB PCR** | • **Specificity**: **High specificity for MTB**<br>• Needs 100 cfu/ml for detection (requires lower load)<br>• PCR based tests are designed to be **specific mycobacterial TB and rifampicin resistance**, **but does not detect other mycobacteria nor predict resistance to other anti TB medications**.<br>• Once the rapid MTB/RIF (Rifampicin) test is reported as MTB detected RIF undetected; this is by definition **NOT a multidrug resistant TB.**<br>• The test is validated to be done on sputum but can be done on non-sputum specimen (However can have false negative tests for the presence of inhibitors).<br>• **A negative test does not rule out TB**. |
| **Culture** (growing a sample) | • **Sensitivity**: **Has the highest sensitivity.**<br>• Needs 1-10 cfu/ml. (few colonies)<br>• Mycobacterial culture is the **most sensitive** however it is a **slow method** (3-6 weeks). The median time for positivity is around 21 days.<br>• **Once positive, additional tests need to be done to identify the species.**<br>• The majority of the developed world uses **liquid/broth culture** of mycobacteria in addition to **solid media (Lowenstein–Jensen slopes or Middlebrook agar).**<br>★ Considered the **Gold standard:**<br>  ○ **Pulmonary TB:** 90-95% sensitive, **Extrapulmonary TB:** much less sensitive<br>• Liquid Culture reduces delays in obtaining results to days rather than weeks for DST, delay may be as little as 10 days vs. 28-42 days with solid media.<br>• Liquid systems are more sensitive increase the case yield by ~10% over solid media.<br>• Liquid systems are more prone to contamination by other microorganisms. |
| **MTB/RIF test** | • Culture-positive TB: Overall sensitivity 97.6%<br>• Smear- and culture-positive sensitivity 99.8%<br>• Smear-negative and culture-positive 90.2%<br>• **Specificity 99.2%** |
| **Histopathology** | • Biopsy from lymph nodes, or other infected body parts.<br>• Typically cause a **caseating granuloma** with a ZN stain for bacilli.<br>• The granuloma formation requires a good immune system to form; therefore this histopathological feature **may not be present in immunocompromised hosts**. |
| **PPD and IGRA** | • **Do not distinguish latent from active TB.**<br>• **Negative test does not rule out active disease**. |

**Chest Imaging**

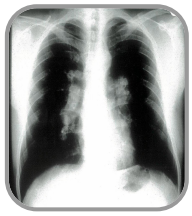
- **Upper lobe/Apical cavity** is typical with surrounding infiltrate + **lymphadenopathy**.



Bilateral pulmonary infiltrate (white triangles), and „caving formation" (black arrows) present in the right apical region, in far-advanced TB.



Apical cavity



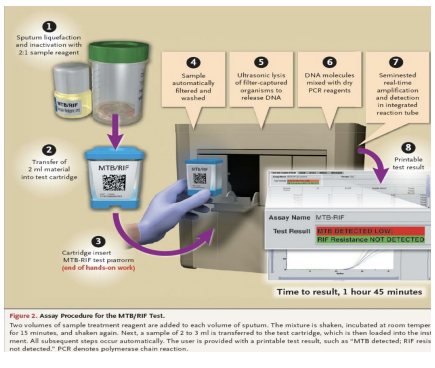
hilar lymphadenopathy

## Microscopy further details...

| | ADVANTAGES/DISADVANTAGES |
|---|---|
| **Fluorescence microscopy (FM)** | • Fluorescence microscopy (FM) detects 10% more TB cases than light microscopy(LM)<br>• Requires only 25% of the time taken to read a Ziehl-Neelsen (ZN) stained smear<br>• FM requires equipment that is expensive and non-robust |
| **Fluorescent Light Emitting Diode (LED) microscopy** | • Inexpensive.<br>• Life span more than 10,000-50,000 hours .<br>• Energy-efficient • Does not require a dark room.<br>• Can be used for both FM and LM with the flick of switch.<br>• Provides bright and clear images.<br>• LED microscopy has 93% sensitivity, 99% specificity compared to conventional LM.<br>• LED microscopy is statistically significantly more sensitive by 6% with no loss in specificity, when compared with direct Ziehl-Neelsen microscopy.<br>• LED microscopy is 5% more sensitive and 1% more specific than conventional FM. |

**• WHO recommends that conventional fluorescent microscopy be replaced by LED microscopy**
**• LED microscopy be phased in as an alternative for conventional ZN light microscopy**

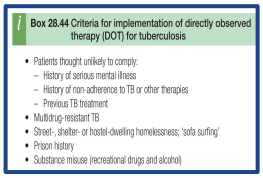
| | ADVANTAGES/DISADVANTAGES |
|---|---|
| **Nucleic acid amplification tests (NAAT)** | -NAATs have high specificity and PPV<br>-Sensitivity is lower and highly variable across studies<br>Sensitivity lower in extra-pulmonary and smear-neg pulmonary TB<br>Negative test does not rule out TB<br>-Expensive<br><br>Cepheid GeneXpert:<br>-All steps automated<br>-Uses cartridges;MTB-specific primers<br>-Result in 2 hours Simultaneous drug susceptibility testing (DST)<br>-Resistance to rifampin uses PCR to amplify an MTB specific sequence of the rpoB gene -In HIV-infected patients it yields up to a 45% increase in tuberculosis case detection compared with smear microscopy |



# Active TB Treatment

## ◀ First line treatment

### 01 General rules:


Box 28.44 Criteria for implementation of directly observed therapy (DOT) for tuberculosis

- Patients thought unlikely to comply:
  - History of serious mental illness
  - History of non-adherence to TB or other therapies
  - Previous TB treatment
- Multidrug-resistant TB
- Street-, shelter- or hostel-dwelling homelessness; 'sofa surfing'
- Prison history
- Substance misuse (recreational drugs and alcohol)

- Daily regimen is more efficacious than intermittent (2 or 3 times a week).
- IN HIV positive, intermittent treatment is associated with **Rifampin resistance.**
- Treatment should be commenced immediately in any patient who is **smear-positive**, and in those who are smear-negative but with **typical chest X-ray changes and no response to standard antibiotics.**
- **Directly observed therapy (DOT)** is essential for assuring completion of TB treatment.
- Patients with active TB must be isolated until sputum is negative for AFB.

### 02 Induction phase *(2 months)*: RIPE

INH and RIF are the main stem of therapy

- **R**ifampicin
- **I**soniazid (Use B6 (pyridoxine) to prevent neurotoxicity of INH)
- **P**yrazinamide
- **E**thambutol

### 03 Continuation phase (*4 months):*

- **Rifampicin + INH for four more months.**

**Extend the continuation phase in the following situations**

| Pulmonary disease | CNS TB | Bone and joint TB |
|---|---|---|
| If **cavitation and culture positive** at the end of the second month of treatment or or bilateral extensive disease; **extend to a total of 9 months.** | Usually **9-12 months** total duration. | **6-9 months** total duration. |

### 04 Corticosteroids indicated in: in two cases only

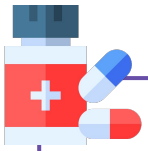
1. **TB meningitis:** improved **morbidity and mortality.**
2. **TB pericarditis:** Previously recommended but recent trials showed no difference in outcome. Can be considered in cases of inflammatory fluid analysis.

# Active TB Treatment

## ◄ ATT side effects[1]

### ❖ Hepatotoxicity:

- ➢ Main ATT: INH, Rif, PYZ.
- ➢ **INH and pyrazinamide are more hepatotoxic than rifampicin. Ethambutol is the least hepatotoxic of all 4 anti TB.** Rifampicin mostly causes cholestatic liver derangement.
- ➢ This is a particular problem when liver function tests become deranged and there is concern about a **drug- induced hepatitis**, in which case it is often necessary to **stop all four drugs and re-introduce one at a time**. **The drug should be stopped only if the serum bilirubin becomes elevated** or if **transferases are more than three times elevated**



#### Rifampicin:

- ○ A **potent enzyme inducer** and decreases the level of other drugs of particular importance **warfarin, antriretroviral therapy** (Integrase inhibitor, protease inhibitors **(PI)** , Nucleotide and nucleoside reverse transcriptase inhibitors **(NNRTI)**) **hormonal contraceptives, corticosteroids.**
- ○ Of the four anti TB drugs, **Rifampicin is the most important** and if it was dropped for side effect or intolerance short course (6 months therapy) can no longer be used.

#### Pyrazinamide:

- ○ Its most common side- effects are **Arthralgias**, **itching** and **rash**, it reduces the **renal excretion of urate** and may precipitate **hyperuricaemic gout.**

#### Ethambutol:

- ○ **Retrobulbar neuritis** (**Color vision** is the first affected, **visual acuity** will later be affected, unlikely to occur with the doses and duration of therapy given in TB, eyes should be regularly asses)

#### Aminoglycosides:

- ○ **Ototoxicity, vestibular toxicity, nephrotoxicity.**

#### Bedaquiline: (new drug)

- ○ A novel drug with a novel mechanism of action **targeting (MTB ATP synthase)**. Approved for pulmonary drug resistant TB when effective therapy cannot be provided.
- ○ **QT prolongation is a serious adverse effect of the medication.**
- ○ Has a long half-life 4 months.

1- The most common side-effects of quadruple TB therapy are **nausea, vomiting, rash and itching.**

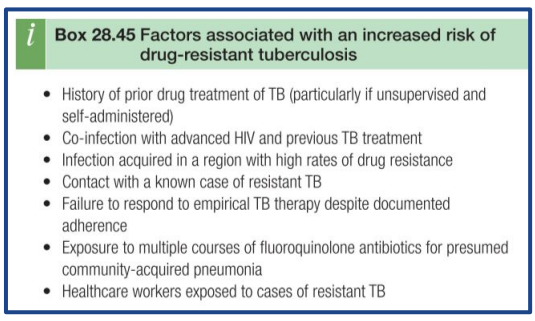
# Active TB Treatment & Resistance

## ◀ Summary of ATT mechanism of action/resistant/ common side effect

| Drug/Dose | Mechanism of action | Mechanism of resistance | Side effect |
|---|---|---|---|
| **Isoniazid**<br>5 mg/kg/day<br>Maximum dose: 300 | - **Inhibits mycolic acid synthesis**.<br>- Penetrates well even to the brain | - Loss of **katG** overexpression.<br>- Alteration in **inhA** encoded reductase | - Hepatotoxicity.<br>- **Peripheral neuropathy** (tingling, pricking, chilling, burning and numbness of the hand) |
| **Rifampin**<br>10mg/kg/day<br>Maximum dose: 600 | **- Inhibits DNA dependent RNA polymerase**, blocking RNA transcript | - **rpoB** (RNA polymerase subunit beta) mutation. | - Rash. Hepatoxicity.<br>- **Thrmobocytopenia**.<br>- Potent enzyme inducer.<br>- Red color of body secretions. |
| **Ethambutol**<br>15mg/kg/day | - **Inhibits arabinosyl transferase enzyme** which will inhibit cell wall arabinogalactan and lipoarabinomannan. | - **embB** gene mutation causing enzymatic alteration in ethambutol binding site. | - Peripheral neuritis.<br>**- (Optic neuritis)**<br>- Hepatotoxicity. |
| **Pyrazinamide**<br>20mg/kg/day | - Unknown.<br>- Pyrizinoic acid lowers the PH below the level necessary for mycobacterial growth. | - **pncA** gene mutation.<br>M. Bovis and M. Leprae are intrinsically resistant. | - Hepatotoxicity.<br>- Asymptomatic **hyperuricemia**.<br>- **Arthralgias** (Polyarthralgia). |
| **Bedaquiline**<br>400 mg daily for 14 days followed by 200 mg thrice weekly to complete 24 weeks. | - **Inhibits ATP synthetase by binding to subunit c.**<br>- Prevents mycobacterium from ATP synthesis and eventually lead to cell death. | - Point mutation in the **atpE** gene, **efflux pump**. **mmpR** mutation. | - QTc prolongation. |

## ◀ Risk factors for drug resistant TB

1. **Contact** with a known case of **drug resistant TB.**
2. Previous **history of treatment** especially if the **patient was non adherent.**
3. **Travel** to an area known to have drug resistant TB (Eastern Europe, South Africa, india).



**Box 28.45 Factors associated with an increased risk of drug-resistant tuberculosis**

- History of prior drug treatment of TB (particularly if unsupervised and self-administered)
- Co-infection with advanced HIV and previous TB treatment
- Infection acquired in a region with high rates of drug resistance
- Contact with a known case of resistant TB
- Failure to respond to empirical TB therapy despite documented adherence
- Exposure to multiple courses of fluoroquinolone antibiotics for presumed community-acquired pneumonia
- Healthcare workers exposed to cases of resistant TB

## ◀ Resistance Definitions

**Multidrug-Resistant (MDR)**

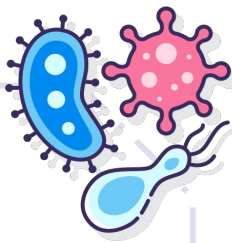
- Resistance to both **Rifampicin** and **INH**.

VS

**Extensively Drug-Resistant (XDR)**

- **MDR** plus resistance to **fluoroquinolones** plus at least one of the injectable 2nd line drugs **(Amikacin, kanamycin, capreomycin).**

# HIV and TB considerations



- HIV increases the risk of progression from latent to active TB.
- CD4 influences the severity and clinical manifestations of TB.
- **TB can increase HIV viral load.**
- **TB is associated with more rapid progression of HIV.**
- In HIV patients it is **less likely to see a cavitary lung disease** (you need good immune system to develop granuloma)
- **With advancing immunosuppression; there is increased risk for:**
  - Smear negative pulmonary TB.
  - Extrapulmonary TB ± Pulmonary disease.
  - CNS TB.
  - Widely disseminated TB/ Mycobacteremia.
- **A negative CXR and a negative smear does not exclude TB.**
- **Extrapulmonary TB, CNS TB and widely disseminated TB are the usual forms in advanced HIV.**

## ◀ HIV-TB Treatment

- Despite the drug-drug interaction rifampicin cause, a **rifamycin based therapy is still the preferred regimen.**
- ART guidelines recommend **efavirenz** based combination **with higher doses of integrase inhibitors.**

| Rifampin | Rifabutin |
|---|---|
| - **Accelerates clearance of PI, NNRTI, INSTI [1], CCR5 inhibitors.**<br>- Integrase inhibitor: Need to give BID dosing.<br>- TAF [2]: If used need to closely monitor HIV viral load while on therapy.<br>**- Should not combine PI with Rifampin.** | - **Weaker enzyme inducer than rifampin.**<br>- A CYP450 substrate (Rifabutin metabolism affected by NNRTI and PIs).<br>- If a PI based ART will be used decrease the Rifabutin dose to 150 mg daily or 300 mg every other day. |

| When to start ART | | | |
|---|---|---|---|
| **CD4< 50** | **CD4< 50** | **HIV infected pregnant women with active TB** | **TB meningitis** |
| **Within 2 weeks** of starting TB treatment. | **Within 8 weeks** of starting TB treatment. | **should be started on ART as soon as feasible** (For maternal health and prevention of mother to child transmission). | ART should not be given until **after 8 weeks** of anti TB medications. |

1- Integrase strand transfer inhibitor
2- Tenofovir alafenamide

# IRIS & Special TB considerations

## ◀ Immune reconstitution inflammatory syndrome (IRIS)

| | |
|---|---|
| **Forms** | • Two forms:<br>  ○ **Paradoxical worsening** of TB when ART is started after TB treatment.<br>  ○ **Unmasking TB** when ART started in setting of not yet recognized TB.<br>• Typically occurs 2 weeks to 3 months after starting ART. |
| **Risk Factors** | • **CD4< 50.**<br>• High pre-ART viral load.<br>• Severe TB<br>• Short interval between initiation of TB treatment and ART. |
| **Protean manifestation** | • Fever, new lesion, extension of prior lesions. |
| **Management approach in IRIS** | • Deal promptly with any limited space issue: (CNS inflammation, obstructing adenopathy), corticosteroid, surgery if needed.<br>• Consider other differential diagnosis<br>• Give **NSAID** in **mild** cases.<br>• **Give corticosteroids in more severe and refractory cases**: Prednisone 1.5 mg/kg/day for two weeks then 0.75 mg/kg/day for two weeks.<br>• **Continue both TB plus ART**. |

## ◀ TB in transplant recipients

- Transplant associated immunosuppression increases the risk of active TB disease if the person is infected.
- Presents atypically and therefore diagnosis is delayed:
  - **One third to half is disseminated or extrapulmonary.**
  - **The ability of granuloma formation is lost by immunosuppression** and therefore patients are unable to contain the infection and they rapidly progress and disseminate.
  - 4% are thought to be donor derived.
- **Can rapidly progress and carry high mortality.**
- Small proportion are donor derived.

### Drug-Drug interactions

- MTOR inhibitors **(Sirolimus/everolimus).**
- Calcineurin inhibitors **(Cyclosporin, tacrolimus).**
- Frequent drug levels of calcineurin and MTORs is advised.
- **Corticosteroid and hence they are at risk for graft rejection.**
- **Rifabutin based regimen is preferred to minimize interaction.**

## ◀ TB and TNF alpha inhibitor inhibits

- **Before putting any patient on TNF alpha, they must be screened for TB first, as they blunt the immune system, thus re-activating latent TB.**
- **TNF alpha inhibitors markedly increase the risk of active TB if infected.**
- Can present with atypical TB (e.g., non-cavitary pulmonary disease, extrapulmonary disseminated).
- **Increased TB morbidity and mortality.**
- Full monoclonal IgG1 monoclonal antibody most potent (i.e., **infliximab, adalimumab, golimumab**).
- **It is recommended to do a PPD or IGRA prior to starting anti TNF:**If any is positive, patient should be started on latent TB management before starting therapy (2 -8 weeks).

# Diagnosis of Latent TB

## ◀ Tuberculin skin test (TST)

- An intradermal inoculation of a mix of antigens causing a delayed type IV hypersensitivity reaction.
- **The induration** caused by the reaction **is measured at 48-72 hours** (positive reaction lasts a few days).
- **Only induration is counted toward a positive test. Erythema is irrelevant.**
- It is an adjunctive in the diagnosis of TB.
- **False positive results may be seen with Nontuberculous mycobacteria (NTM) or prior BCV vaccine.**
- **False negative** (anergic) tuberculin skin tests (TSTs) are common in patients with **immunosuppression** due to **HIV infection (CD4+ <200/mm3)**, those taking immunosuppressant medications (**chemotherapy**, **anti-TNF therapy, steroids**), those at the **extremes of age and those with active disease.**
- A booster effect can be mistaken for positive PPD test:
  - TST maybe initially negative if there is a remote history of infection. However, TST stimulates immune response to MTB antigens and a subsequent TST can be positive and mistaken for seroconversion.
  - For that, a **2 step TST** for individuals who may be tested periodically (e.g., HCW). However, if the first test is positive, a second test is not necessary.

❖ **Cutoffs are based on likelihood of true exposure, risk of progression to active TB if infected (5 mm; 10 mm; 15 mm)**

| Latent TB infection (LTBI): Classification of Tuberculin Skin Test (TST) Results: | | |
|---|---|---|
| **≥5 mm is Positive in:** | **≥10 mm is Positive in:** | **≥15 mm is Positive in:** |
| • HIV Infected.<br>• Recent TB contact.<br>• CXR with fibrotic changes.<br>• Organ transplantation.<br>• Prednisone ≥ 15mg/d x1 month or more.<br>• TNF alpha antagonists. | • Recent arrival **(within 5 years)** from TB high prevalence area.<br>• Injection drug use.<br>• Residents and employees of high risk settings (HWC, corrections & home shelters).<br>• Myobacteriology lab staff.<br>• **Children <5 years old.**<br>• Medical conditions: Diabetes, silicosis, end stage renal disease, gastrectomy or small bowel bypass, solid organ transplant, CA head and neck. | • Persons with no known risk factors for TB. |

## ◀ Interferon gamma release assays- IGRA

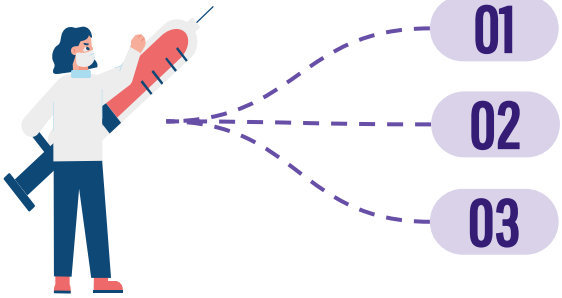
**Now replacing tuberculin skin test**

- Two tests are currently available:
  - QuantiFERON-TB
  - T-SPOT.TB.
- **Blood based**, in vitro stimulation of WBC with protein antigens specific for M. TB.
- **The advantage of IGRA over PPD is that there is no cross reactivity with BCG vaccine.**
- IGRA is **as sensitive** as PPD **but more specific**.
- **False Positive: caused by M. Kansasii and M. Marinum.**
- **False Negative: in immunocompromised**.
- The test does not differentiate between active and latent infection.
- **TST** remains the **first choice in children**, while **IGRA** represents the **first choice for individuals with HIV.**

# Management of Latent TB & BCG Vaccine

## ◀ Management of latent TB[1]

- **Excluding active TB is a key component of the diagnosis of latent TB infection**:
  - **Review of system**: Fever, weight loss, cough, night sweats, focal signs/symptoms that could be associated with extrapulmonary TB).
  - **Chest X-ray to exclude occult pulmonary TB**.
  - Previous BCG has no effect on the following recommendations.
- **Preferred Regimens for latent TB include:**



01
- **Rifampin daily for 4 months.** (frequently used)

02
- **INH + Rifapentine once weekly for 12 doses .**

03
- **INH + Rifampin daily for 3 months.**

- **Alternative**: INH daily for 6 or 9 months.
- Rifampin + PYZ is **NO longer used** because of the risk of hepatotoxicity.
- **Perform LFTs prior to treatment** in adults with risks for hepatotoxicity (Ethanol, risk for viral hepatitis, other hepatotoxic medications).
- **Monthly review of systems for adverse effects**:
  - **Peripheral neuropathy if on INH (Can be avoided by B6 supplements).**
  - **Hepatotoxicity** (Nausea/vomiting, abdominal discomfort, jaundice).

## ◀ BCG vaccine

- Live attenuated vaccine (from M. Bovis).
- **It should not be administered to those who are immunocompromised (e.g. HIV) or pregnant**

### Neonatal vaccination

- **Decreases the incidence of severe forms of childhood TB.**
- **No to very limited impact on adult TB.**
- **Regional lymphadenitis can occur after vaccination**, typically no treatment is indicated.
- **Disseminated infection can occur in immunocompromised** (Treatment is needed).

### Immunotherapy for bladder cancer

- **Intravesicular administration**.
- **Complications**:
  - Contemporaneous with BCG treatment or up to years later.
  - Granulomatous prostatitis, Hepatitis, Epididymitis-orchitis, Spondylitis, psoas abscess, military pulmonary, disseminated/sepsis.
- **Treatment:**
  - Inherent resistance to PZA; treat with rifampin + INH + Ethambutol.

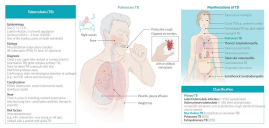
1- In certain groups with latent TB infection, chemoprophylaxis is offered to reduce the risk of active infection:
- Household and close workplace **contacts of patients with pulmonary and laryngeal TB**, **health workers**, recent new **migrant entrants from high-risk countries**, patients who are **immunocompromised (e.g. HIV infection)**, those about to commence treatment with **biologic agents (such as infliximab)**, those due to have **stem cell or solid organ transplants.**

# Summary "From Step Up"

## Tuberculosis Summary

### Overview

- Tuberculosis is a bacterial infection caused by **Mycobacterium tuberculosis**
  - **Mycobacteria are acid-fast bacilli (AFB)—considered slow growing but hardy organisms.**
- It is a world wide disease, infecting more than 1.7 billion causing 3 million deaths per year.



### Transmission

- By inhalation of aerosolized droplets containing the active organism.
- Only those people with active TB are contagious (e.g., by coughing, sneezing).

### Pathophysiology

**Primary TB:**
- Bacilli are inhaled and deposited into the lung, then ingested by alveolar macrophages
- Surviving organisms multiply and disseminate via lymphatics and the bloodstream.
- Granulomas form and "wall off" the mycobacteria.
- After the resolution of the primary infection, the organism remains dormant within the granuloma.
- Only 10% of individuals with primary TB will develop active disease in their lifetime.

**Secondary TB (reactivation):**
- Occurs when the host's immunity is weakened (e.g., HIV infection, malignancy, Immunosuppressants, substance abuse, poor nutrition).
- Usually manifests in the most oxygenated portions of the lungs (Apical/Posterior segments).
- Produces clinical manifestations of TB.
- Can be complicated by hematogenous or lymphatic spread, resulting in miliary TB.

**Extrapulmonary TB:**
- Individuals with impaired immunity may not be able to contain the bacteria at either the primary or the secondary stage of the infection.
- This may result in active disease throughout the body (TB lymphadenitis (25%), Pleural TB, Skeletal TB, TB meningitis)

### Risk factors

- HIV-positive patients
- Recent immigrants
- Prisoners
- Close contacts of someone with TB
- Diabetics
- Healthcare workers
- Glucocorticoid use
- Hematologic malignancy
- Alcoholics & Injection drug users

### Clinical features

**Primary TB:**
Usually asymptomatic
Pleural effusion may develop

**Secondary (active) TB:**
Constitutional symptoms: Cough, fever, night sweats, weight loss, and malaise.
- Cough progresses from dry cough to purulent sputum.
- Hemoptysis suggests advanced TB

**Extrapulmonary TB:**
May involve any organ. (eg. lymph nodes, pleura, genitourinary tract, spine, intestine, and meninges ).
Miliary TB refers to hematogenous dissemination (Common in HIV patients).

### Diagnosis

Must have a high index of suspicion, depending on patient's risk factors and presentation.

**Chest X-Ray (CXR):**
- Classic findings are upper lobe infiltrates with cavitations
- Other possible findings:
  - Pleural effusion(s)
  - Ghon complex and Ranke complex: evidence of healed primary TB
  - Atypical findings common in immunocompromised patients

**Sputum studies:**
- Definitive diagnosis is made by sputum culture (takes 4 to 8 weeks)
  - three morning sputum specimens
- PCR can detect DNA more rapidly
- Diagnosis is sometimes made by AFB on microscopic examination, but not definitive

**Tuberculin skin test (PPD test):**
Not for diagnosis of active, if +, a chest x-ray is used to diagnose active TB
Measure induration 48-72 hours
≥15 mm in patients with no risk factors.
≥10 mm in for risk groups.
≥5 mm for + HIV, steroid users, organ recipients, close contacts of those with ACTIVE TB, or radiographic evidence of primary TB.

### Treatment & Prevention

**First line therapy:**
**4 drug regimen**: (2 months)
- isoniazid (INH) - Rifampin Pyrazinamide - Ethambutol or - Streptomycin

**Then** INH & Rifampin (4 months)

**Prophylactic treatment** for latent TB (i.e., +PPD skin test): **INH for 9 months**
- active TB has been excluded (negative CXR, sputum, or both).

**Drug failure:**
- Non compliance.
- Inappropriate drug.
- Drug resistance.

# Lecture Quiz

**Q1: A 56-year-old woman who immigrated from China 3 years ago comes to the emergency department because of substantial hemoptysis . Initial work up includes a chest x-ray which shows several cavitary lesions in the upper lung fields bilaterally. Further testing confirms a diagnosis of tuberculosis . Proper airborne precautions are initiated and the patient is placed in isolation . Which of the following is the most appropriate initial treatment , assuming the TB strain is not multi-drug resistant?**

A- Administration of isoniazid
B- Administration of rifampicin and isoniazid
C- Combination therapy with rifampicin, isoniazid and ethambutol
D- Combination therapy with rifampicin, isoniazid, ethambutol and pyrazinamide

**Q2: An 18-year-old man presents to the urgent care clinic. He has recently immigrated and has been experiencing back pain for a few weeks. He slipped on ice and had a minor fall onto his backside around the time that the pain began, but he does not believe it was severe enough to have caused serious damage. The pain radiates from the lower back to the gluteal muscles, back of the upper thigh, posterior lower limb, and feet. He has fever (38.5oC) and has noticed recent weight loss. What is the most likely explanation for this condition?**

A- Mycobacterium tuberculosis co-infection with HIV
B- Infection of lower thoracic and upper lumbar vertebrae
C- Infection of the cervical spine
D- Herniated disc and Pott's fracture of the ankle as a result of the fall

**Q3: A 57-year-old woman comes to the clinic because of persistent coughing productive of blood-tinged sputum . She has had night sweats and chills for the past week. She is a nurse working on the infectious disease unit of the hospital. Her temperature is 37.5°C (99.5°F), pulse is 82/min, respirations are 18/min, and blood pressure is 120/80 mm Hg . A blood sample is drawn for quantiferon testing. Chest x-ray shows right hilar lymphadenopathy . Which of the following is most likely present in the affected lymph nodes of the lung??**

A- Fibrinoid necrosis
B- Liquefactive necrosis
C- Caseous necrosis
D- Coagulative necrosis

**Q4: A 24-year-old woman comes to the office because she forgot to take appropriate precautions while volunteering at a hospital and interacting with an HIV-positive patient being treated for active infection with Mycobacterium tuberculosis . Her past medical history is noncontributory and she is a healthy medical student. Physical examination shows the patient is anxious with no other abnormalities. A PPD is placed. Two days later, she calls, saying her arm has 6 mm of induration around the injection site, and she is horrified because she remembers that the patient had initially presented with only 5 mm of induration. Which of the following most accurately describes the criteria for tuberculin positivity in this student?**

A- PPD+ if induration ≥10 mm
B- PPD+ if induration ≥15 mm
C- PPD+ if induration ≥5 mm
D- PPD+ if induration ≥6 mm

**Q5: A 36-year-old man comes to the emergency room complaining of a mass on the right side of his neck which has been growing over the past 3 months. He has also experienced a heavy cough for the same period of time . On examination, the mass is fluctuant, non-tender, and cold to touch. His temperature is 38.7°C (101.6°F), pulse is 83/min, respirations are 18/min, and blood pressure is 110/72mmHg. His past medical history includes HIV , for which he is on anti-viral treatment. Fine-needle aspiration of the cervical mass allows for staining, which shows acid-fast bacilli and granulomatous cells with caseous necrosis . Which of the following is the most likely cause of his cervical mass?**

A- Tuberculous lymphadenitis
B- Nasopharyngeal carcinoma
C- Papillary thyroid cancer
D- Branchial cleft cyst

Answers: Q1:D | Q2:B | Q3:C | Q4:C | Q5:A

Answers Explanation File!

# GOOD LUCK !

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