Tuberculosis

20/10/2024

Dr. Sulaiman Mahmoud Bani Abdel-Rahman

MBBS - Mutah University

MSc Medical Microbiology – University of Manchester

PhD Medical Virology - University of Manchester

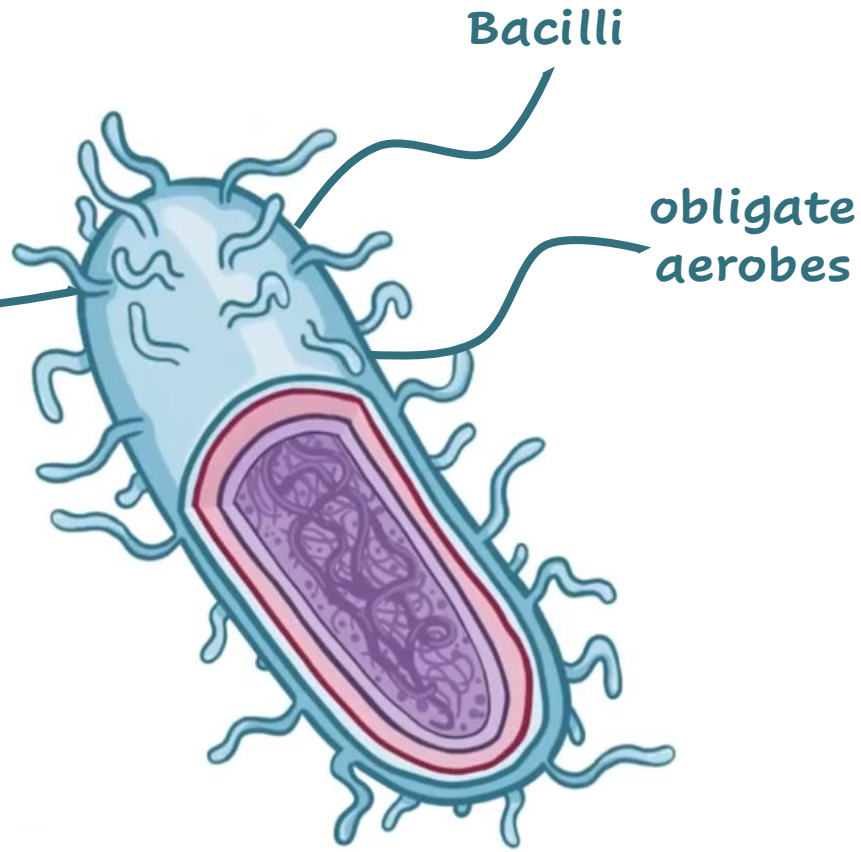
Tuberculosis - General characteristic

1. Weakly Gram-positive bacilli
2. Nonmotile, obligate aerobes
3. Nonspore forming
4. The lipid mycolic acids, make up more than 60% of the total cell wall mass (for which the mycobacteria are named)
5. Facultative intracellular pathogens usually infecting phagocytes (e.g. macrophages).

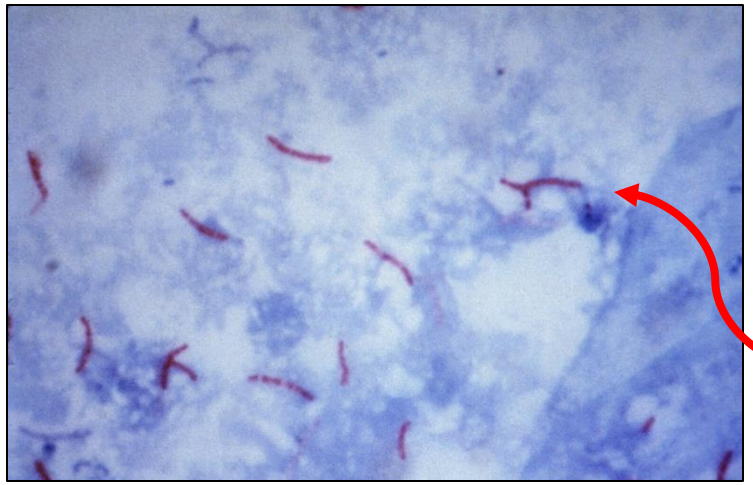
Tuberculosis - General characteristic

Waxy Cell Wall

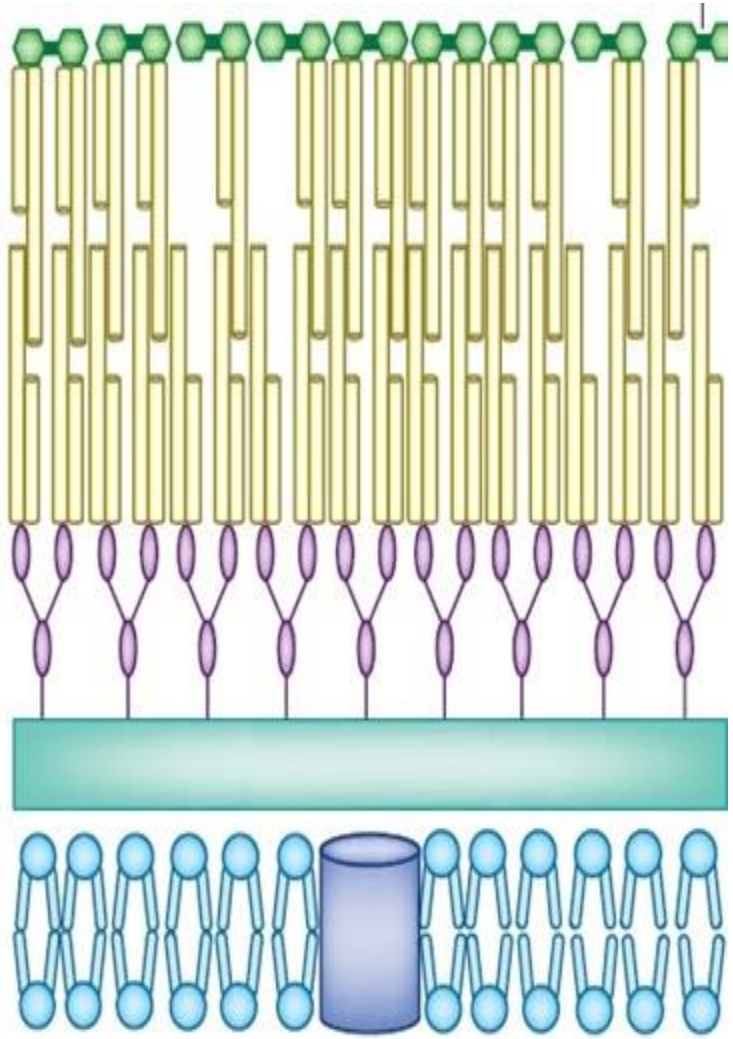
- Thick Mycolic acid layer
- Acid-Fast



Ziehl-Neelsen stain



Tuberculosis - General characteristic



Mycolic acid: It confers very low permeability to antibiotics and responsible for acid fastness

Arabinoglycan a highly branched polysaccharide, serves to **connect peptidoglycan with the outer mycolic acid layer**

Peptidoglycan : maintains the regigidity of the cell wall

Plasm membrane

Tuberculosis – Transmission & Risk Factors

Source of Infection:

- Human (e.g. cases of pulmonary tuberculosis)
- Bovine (e.g. consumpion of unpasturized milk)

Mode of infection

1. **Inhalation mode:** tuberculosis is an airborn disease transmitted by inhilation of droplet nuclei while coughing and sneeezing, or spaking of infectd patients. The tiny dry droplets that contains bcateria (<5 µm in diameter) may remains suspended in the air for several hours.
2. **Inoculation mode:** the trasmission through direct skin contact with a infectd patiens is uncommon.

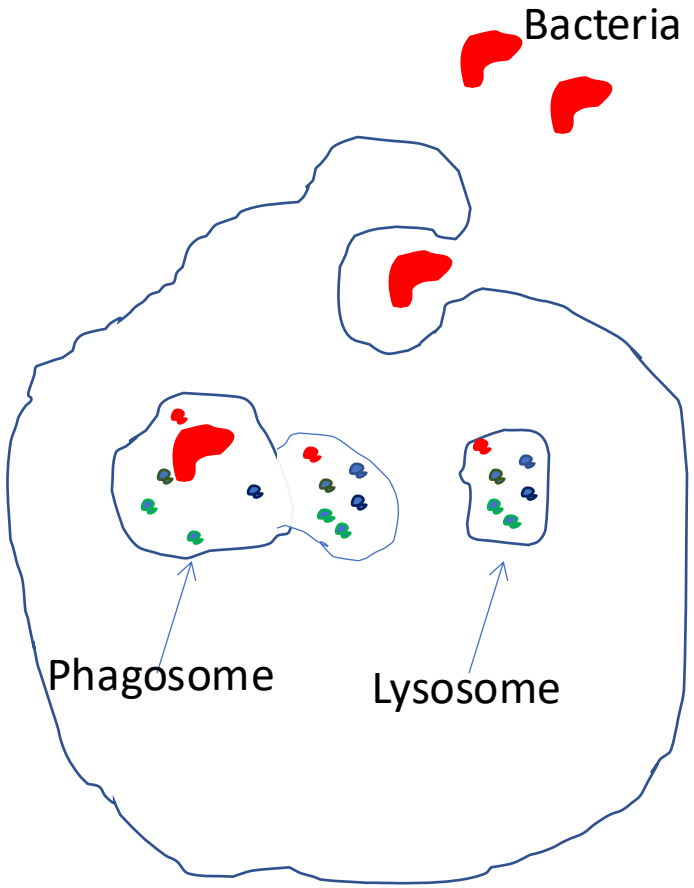
Risk factors

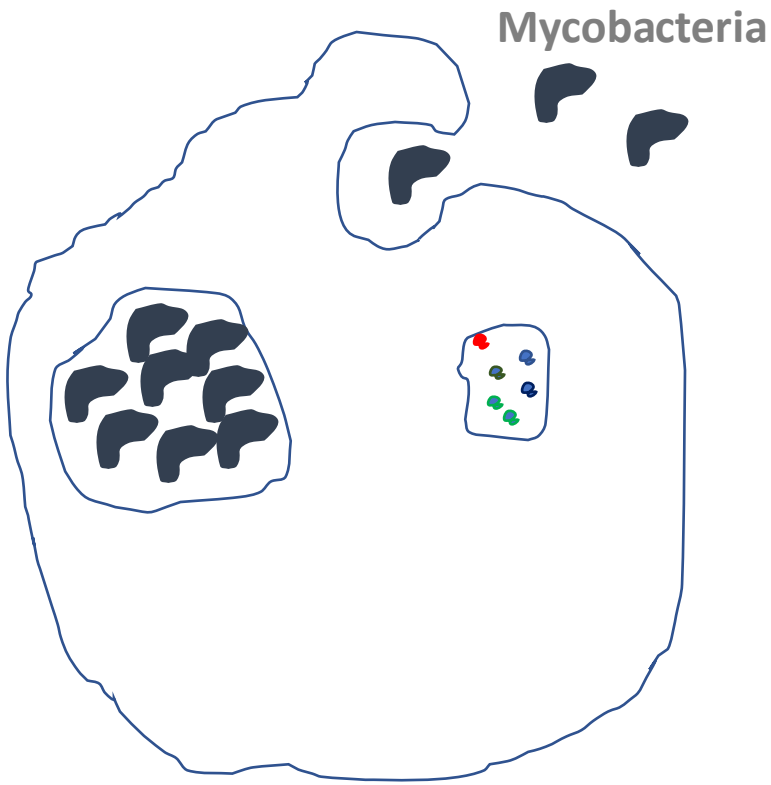
- Low immunity patients (AIDS)
- Posttransplantaion (renal, cardiac), diabetes, smoking, IV drug abuse, chronic renal failure

Tuberculosis – Epidemiology

- TB is the **second-most common** cause of death from infectious diseases **after AIDS.**
- **The infection dose (ID) 10 organisms.**
- 1/3 of the global world population is infected.
- 7-9 million new cases / year.
- Mortality without specific therapy: 70% of smear positive patients within 10 years.
- 2000-2020 one billion people were infected.
- 2000-2020: 35 million people died.
- Source of epidemics involve **school children and teachers** with unrecognized pulmonary tuberculosis, **homeless shelters, nursing homes, and health workers exposed to patients with unrecognized tuberculosis**.

Q: Why Mycobacteria are can survive inside macrophages

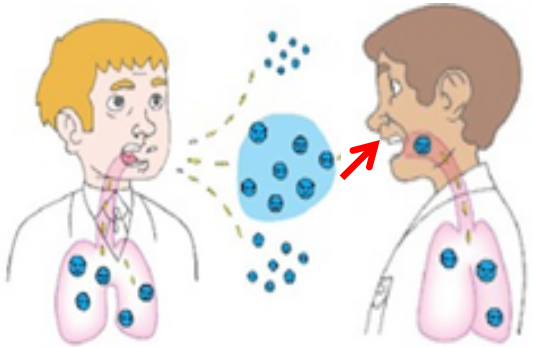




- Mycobacteria inhibits phagosome lysosome fusion **(Sulfatides factor)**
- Bacteria will multiply
- Macrophage will burst
- Proteolytic enzymes will released outside causing tissue destruction

Pathogenesis of TB

Classification of tuberculosis



Exposure

1° infection

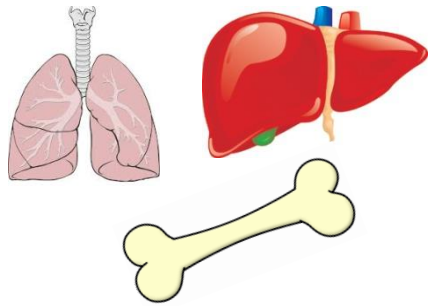
95%

Healing

5%

Local pulmonary progression

Miliary TB



5% undergo 2° TB (reactivation)

Due to

- HIV
- Transplantation
- DM
- Smoking
- Others

Primary TB

1. Primary tuberculosis is the response to the initial infection in an individual **not previously infected and sensitized** to *Mycobacterium*
2. Droplet containing tubercle bacilli are deposited in the peripheral respiratory alveoli
3. Tubercle bacilli are engulfed by alveolar macrophages.
4. The majority of individuals show resistance to infection and are able to contain the infection
5. Macrophages are activated by the cytokines at the site of infection. They be will able to kill and digest the tubercle bacilli.
6. These activated macrophages will aggregate around the center of the lesion and form a characteristic granuloma called tubercles

Primary TB

GHON Focus

+ Hilar lymph nodes

GHON Complex

*** Signs of infection after exposure**

- Mostly Asymtomatic
- Or Flu-like symptoms

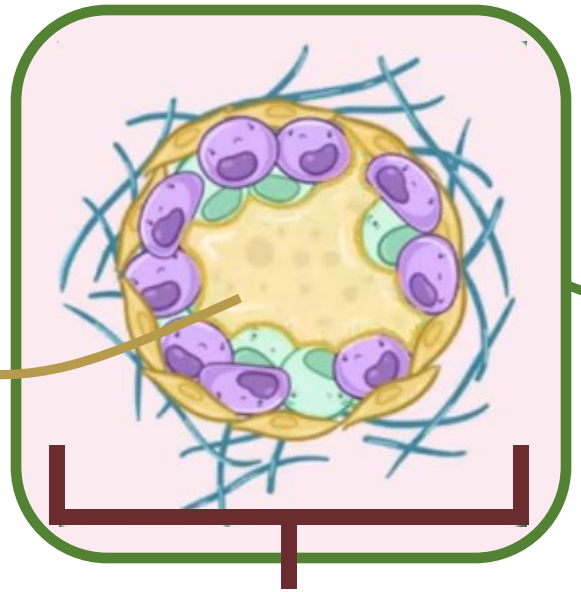
*** ~ 3 weeks → cell-mediated immunity**

Immune cells surround the TB infection

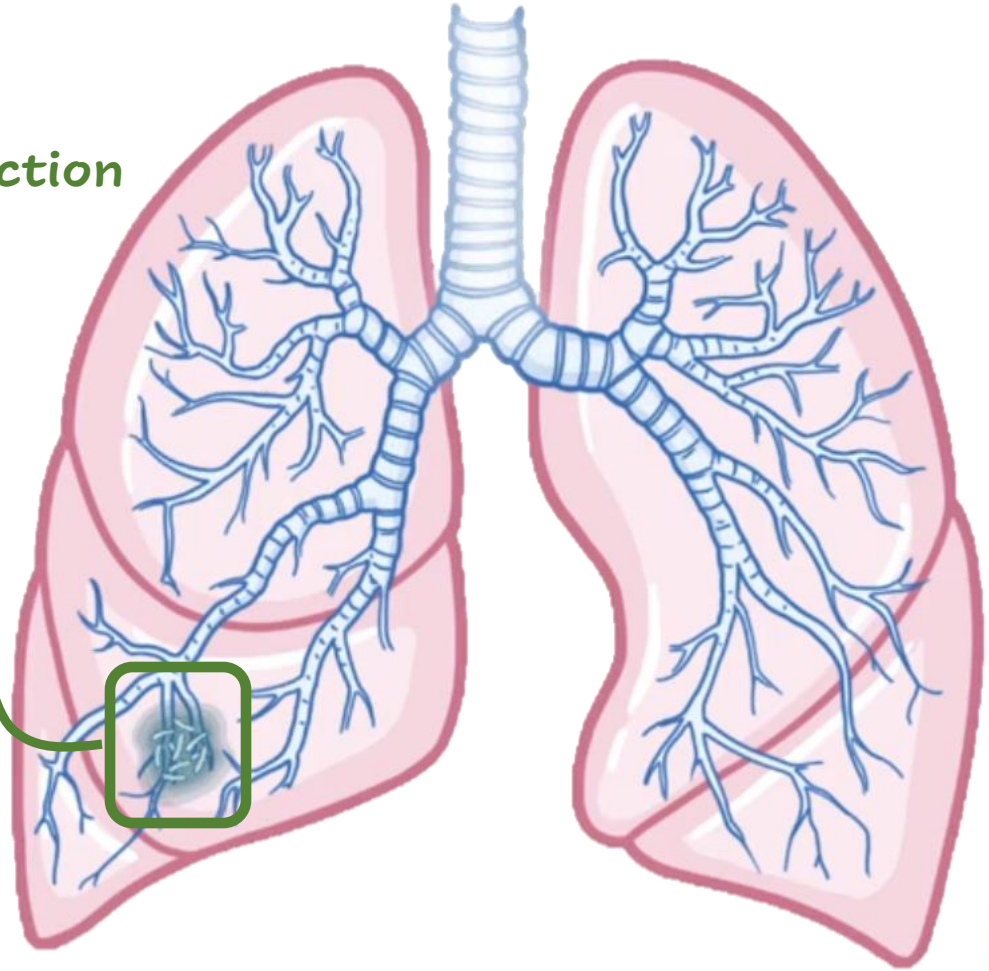
Granuloma

- Wall off Bacteria and prevent spreading

Caseous Necrosis



GHON Focus



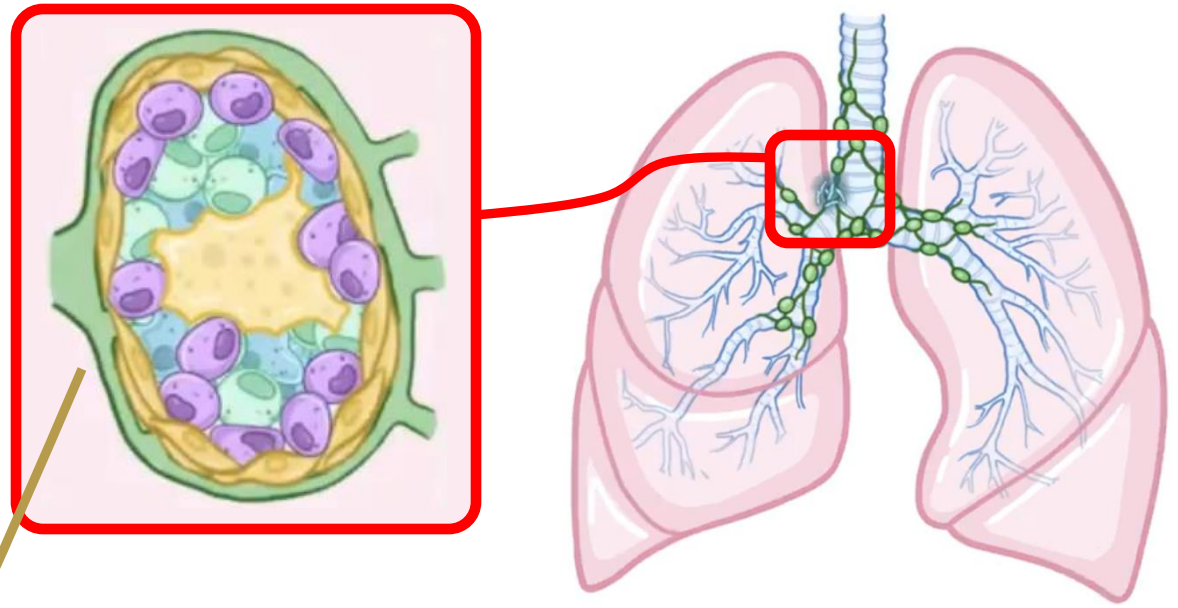
TB travels to the hilar lymph nodes

- Carried over by immunes cells via lymph
- OR direct extension of Ghon focus

GHON Focus

+ Hilar lymph nodes

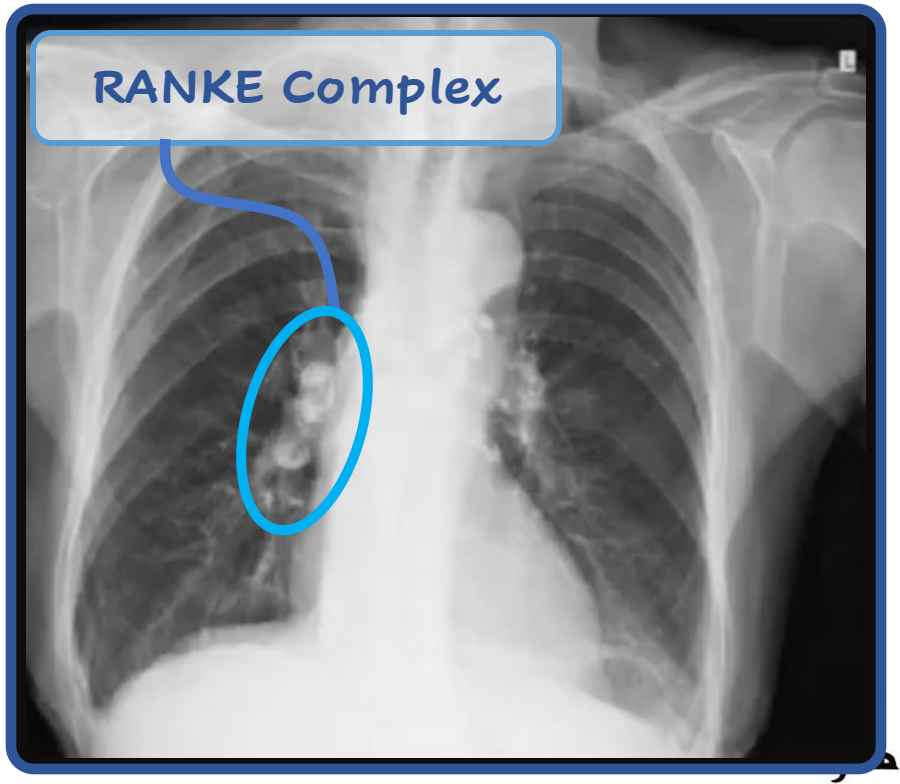
GHON Complex



Tissue encapsulated within the granuloma

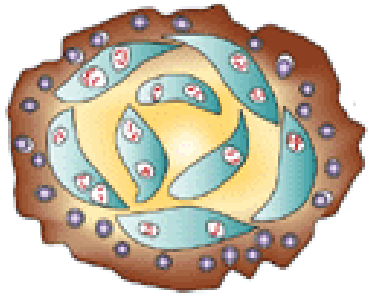
- Fibrosis
- & maybe Calcification

Produce Scar that can be seen on X-Ray



Pathogenesis of TB

Primary TB



Types of granulomas:

A. **Hard tubercles**: tubercles are initially hard, composed of a central zone of activated macrophages (epithelioid and giant cells) and peripheral zone of lymphocytes and fibroblast

B. **Soft tubercles**: later the central part of the lesion undergoes caseous necrosis, and in contains necrotic tissues resembling soft cheese

Growth of the *M .tuberculosis* is inhibited within this necrotic environment because of low oxygen tension and low pH. Eventually the lesion heals and calcifies. The viable bacilli may remain dormant within the macrophages or within necrotic material for many years without causing further tissue destruction

In a minority of cases, especially associated with the risk factors the macrophage activating response will be weak and the bacilli will be more virulent leading to secondary and reactivation infection.

Secondary TB

* Some Cases
  - TB is killed by the immune system
  - نهاية سعيدة

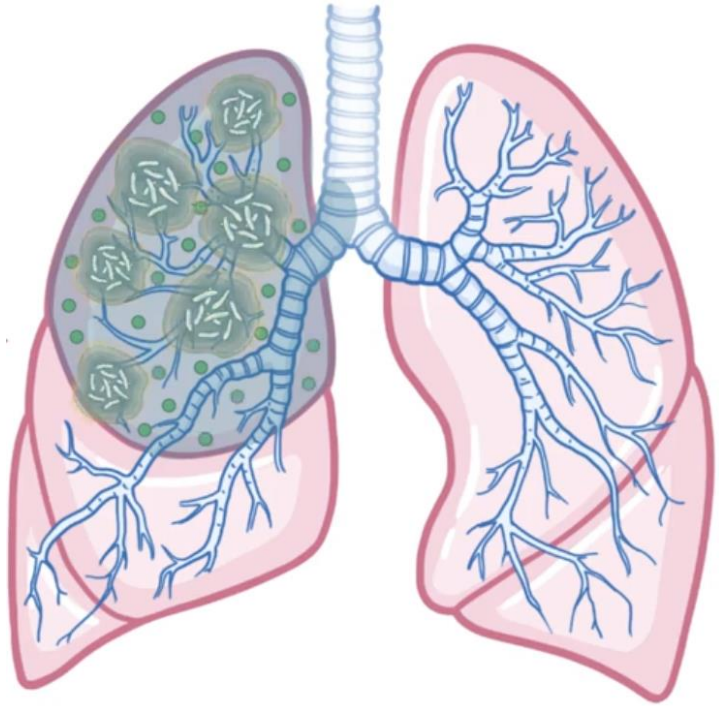
* Other Cases
  - TB remains viable even TB is walled off
  - Alive BUT **dormant**

Reinfection OR Immune system compromised (AIDS, chemotherapy, etc)

Reactivation

Patient is previously exposed → Strong immune response → memory T cells release Cytokines (massive) to control the infection

More Areas of Caseous necrosis → Cavities



Primary TB - Manifestations of Primary TB

- The primary stage of the disease may be symptom-free, or the individual may experience a flu-like illness.
- Patients develop flu-like illness (cough, fever, night sweats, weight loss etc). This can lead to delays in seeking care, and results in transmission of the bacteria to others.
- Healing in 3 weeks with fibrosis ± calcification

Secondary (reactivation) tuberculosis

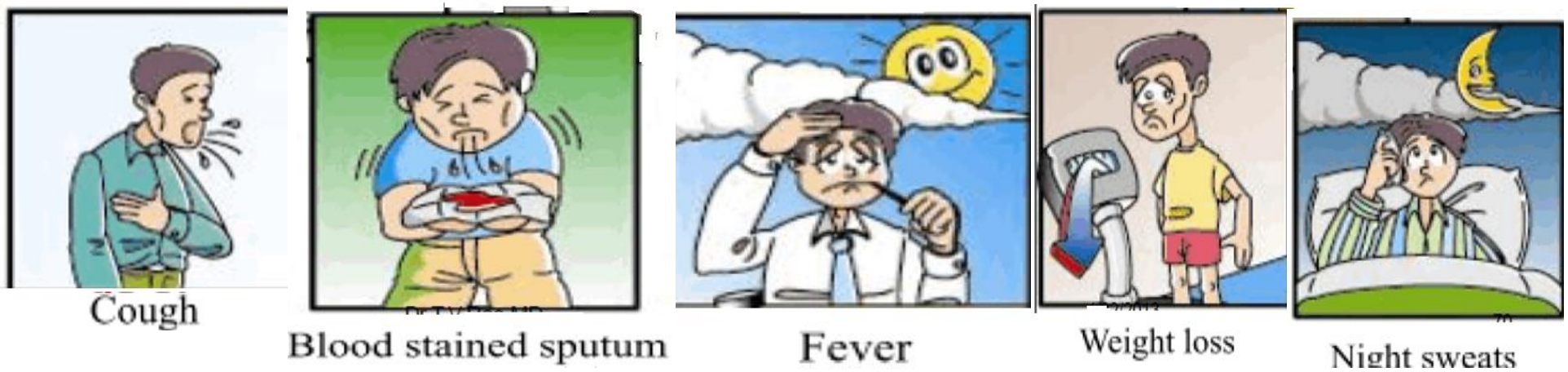
1. Occurs in 5% of patients had primary tuberculosis
2. The risk factors associated with **reactivation including**
   A. Weakened immune system including:
      - HIV/AIDS
      - Diabetes
      - Certain cancers
      - Cancer treatment, such as chemotherapy
      - Drugs to prevent rejection of transplanted organs
      - Malnutrition
   B. Poverty and drug abuse
   C. Smoking
3. Reactivation usually occurs in body areas of relatively high oxygen tension and low lymphatic drainage, most often in the apex of the lung.

Secondary (reactivation) tuberculosis (Cont.)

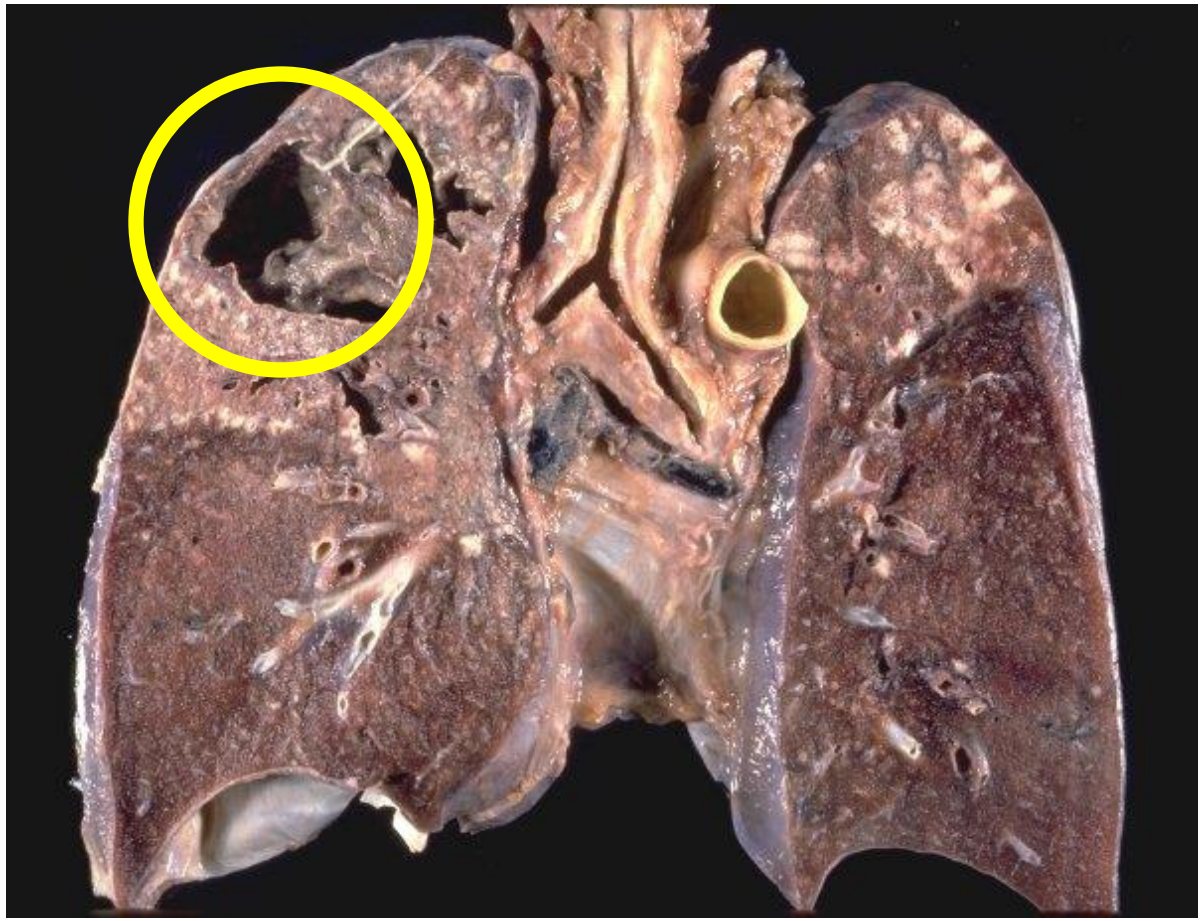
4. The caseous necrosis become liquefied which containing a large number of bacilli which further spread by three ways:
   - Direct drainage into the airways and then get discharge into the environment while coughing and talking
   - Lymphatic spread
   - Hematogenous spread to various organs
5. The lesions show spreading and resulting in a large pulmonary cavity and bronchial spread

Manifestations of secondary TB

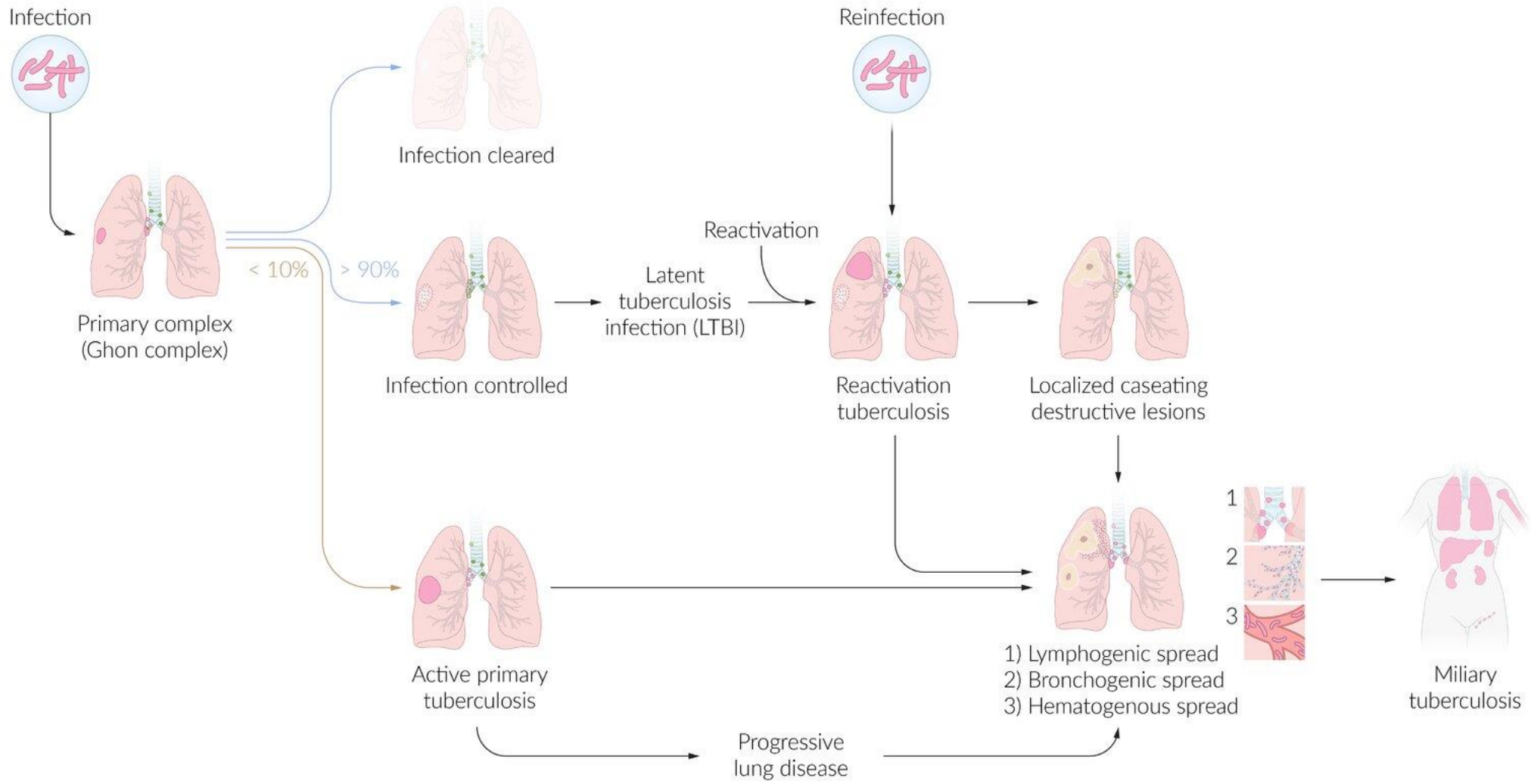
1. Cough is the common symptom
2. It is initially dry, but as the disease progresses sputum is produced and mixed with blood (hemoptysis).
3. Fever, malaise, fatigue, sweating, and weight loss
4. Radiographically, lung cavities with progressive destruction of lung tissue.



Lung cavitation



Outcomes

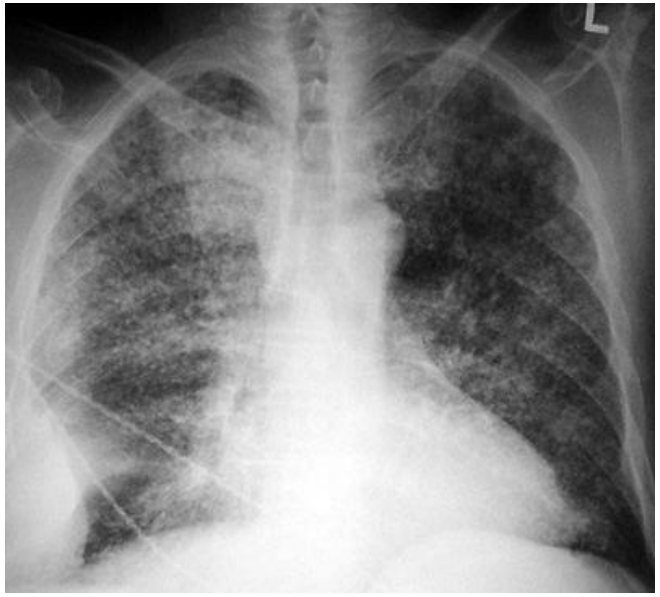

Infection
Infection cleared
Reinfection
Primary complex
(Ghon complex)
< 10%
> 90%
Infection controlled
Latent
tuberculosis
infection (LTBI)
Reactivation
Reactivation
tuberculosis
Localized caseating
destructive lesions
Active primary
tuberculosis
1
2
3
1) Lymphogenic spread
2) Bronchogenic spread
3) Hematogenous spread
Miliary
tuberculosis
Progressive
lung disease

Outcomes

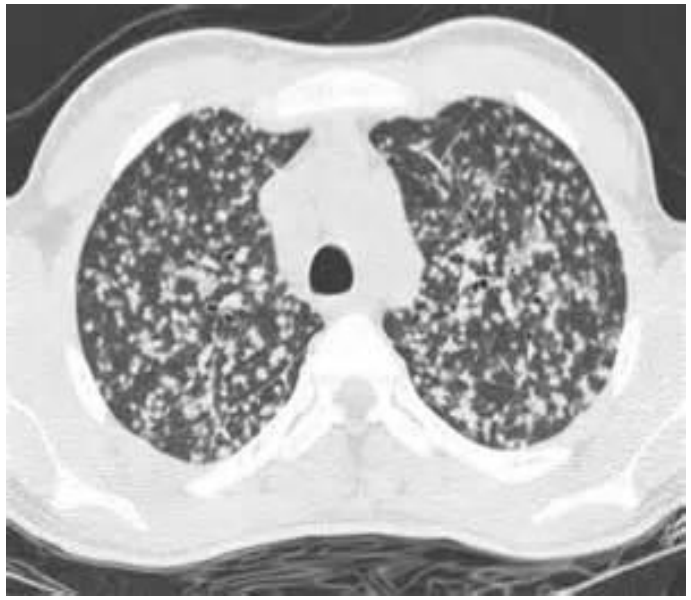
- **Local Progressive Pulmonary TB**
  1. This can occur after primary or secondary TB
  2. Occurs by the local extension to an entire lobe or segment
- **Disseminated (miliary) TB**
  1. Miliary pulmonary disease
  2. Spread through trachea to larynx leads to Laryngeal TB
  3. Swallowing infected sputum leads to intestinal TB
  4. Spread through pulmonary veins → Heart → arteries → systemic miliary TB.

Pathogenesis of TB

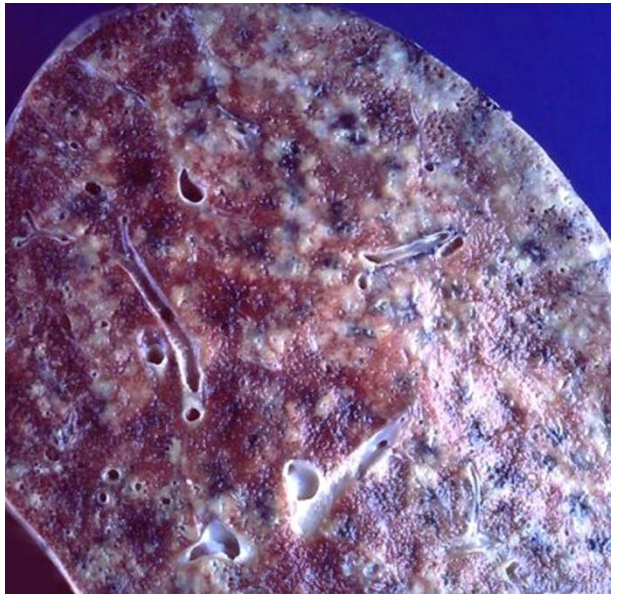
Miliary TB



X-ray of lung with miliary TB

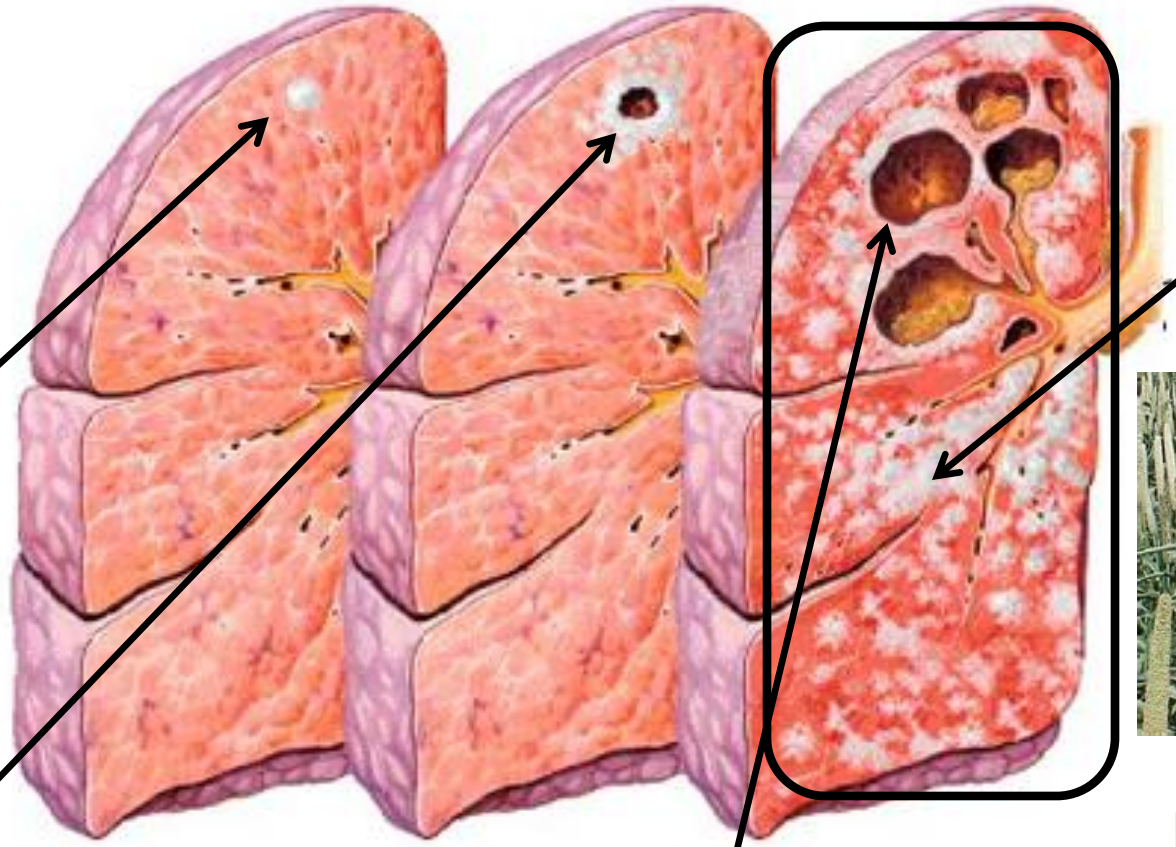


CT scan of lung with miliary TB



Lung miliary TB

Pathogenesis of TB



Primary TB

Miliary TB

Secondary (reactivation) TB

✓Progressive Pulmonary TB (entire lob)

Millet

Millet seeds

When to suspect TB infection?

"Any person who presents with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks)."

Diagnosis – Active TB

Sample Type:

1. In pulmonary tuberculosis:
   - Sputum samples (most common) : Obtain ≥ 3 samples separated by 8 to 24-hour intervals (should include at least one early morning sample).
   - Gastric lavage → Usually indicated in children who are unable to expectorate
   - Bronchoalveolar lavage → Bronchoscopy is indicated if induced sputum or gastric lavage samples are insufficient.
2. In extrapulmonary tuberculosis (depending on the site of infection):
   - Lymph node aspirate, Pleural fluid, Urine, Synovial fluid, CSF

- **Microbiological tests for active TB**
  - Acid-fast bacilli smear microscopy→ Ziehl Neelsen stain or auramine rhodamine stain
  - PCR → for confirmation of AFB positive smears
  - Culture → Gold standard diagnostic test BUT Takes 2 to 6 weeks for positive cultures to develop
- **Imaging studies:** CXR or CT scan

Diagnosis – Latent TB

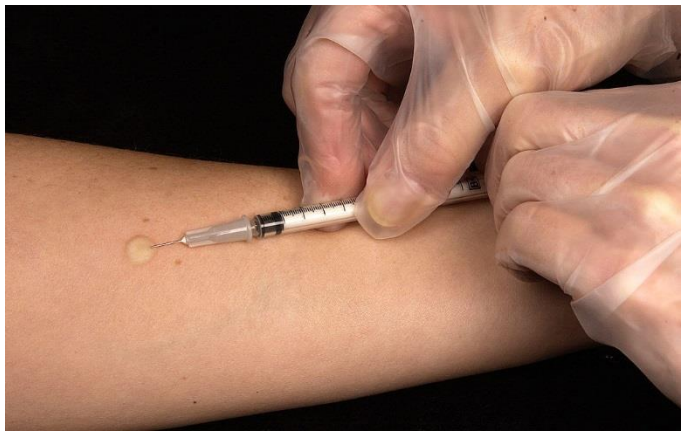
- **Interferon-γ release assay (IGRA)** → preferred in those who have had the BCG vaccine
  - An ELISA test that measures the level of interferon-γ expressed by T cells after coming into contact with Mycobacterium tuberculosis.
  - In contrast to tuberculin skin testing, there are no false-positive results with IGRA in patients who received the Bacillus Calmette-Guérin (BCG) vaccine.
- **Tuberculin skin test** (purified protein derivative test, Mantoux test)
  - Latent tuberculosis is diagnosed by demonstration of type IV (delayed) hyoersensitivity rection against the tubercule bacllic antigens

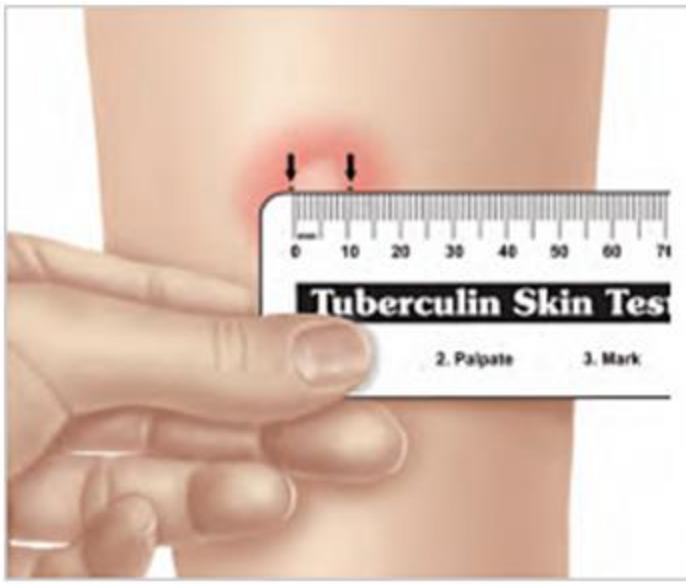
Tuberculin skin test

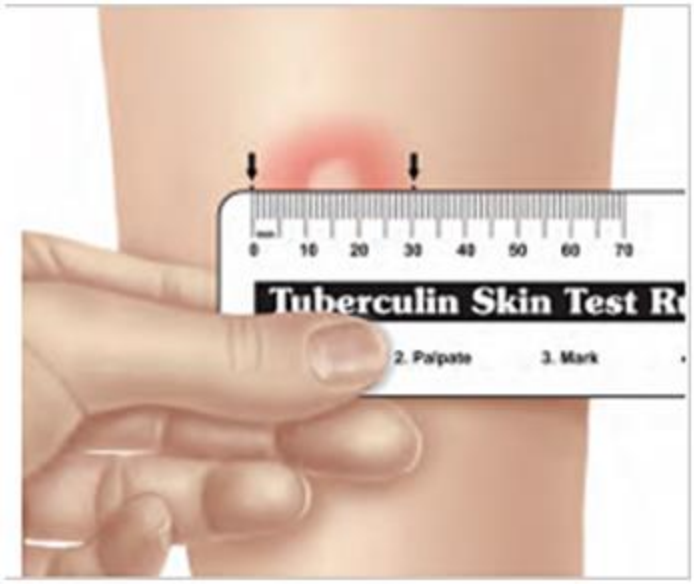
- **Principle**
  - Latent tuberculosis is diagnosed by demonstration of type IV (delayed) hypersensitivity rection against the tubercule bacllic antigens
- **Antigens used in tuberculin test**
  - PPD (purified protein derivative antigen): it is a purified preparation of the active M. tuberculosis proteins after growing on a semisynthetic medium
- **Reading**
  - It is taken after 48-72 hours. At the site of inoculation, and induration surrounded by erythema is produced. If the width of induration is:
    - ≥ 15 mm: Positive (tuberculin reaction)
    - 6-9 mm: Equivocal/ doubtful reaction
    - < 5 mm: Negative reaction

Tuberculin skin test

Mantoux test







Reading the Mantoux tuberculin skin test: (left, correct) only the induration is being measured; (right, incorrect) the erythema is being measured.

Screening tests for LTBI (Self Study – not part of your exam except the red coloured text) Source: amboss.com		
	Tuberculin skin test (purified protein derivative test, Mantoux test)	**Interferon-γ release assay** (IGRA)
Mechanism	• Tests cell-mediated immunity against *M. tuberculosis* via delayed hypersensitivity reaction (type IV HSR) mounted by T cells	• Tests cell-mediated immunity against *M. tuberculosis*-specific antigens by measuring the amount of IFN-γ released by T cells using ELISA
Procedure	• Step 1: 0.1 mL (or 5 units) of purified protein derivative (PPD) injected intradermally on the volar surface of the forearm resulting in wheal formation • Step 2: transverse diameter of **palpable induration** checked 48–72 hours later	• One sample of whole blood is required.
Benefits	• Inexpensive • Preferred test in children < 5 years of age	• Only requires a single office visit • Preferred test in individuals with prior BCG vaccination • Results are available within 24 hours.

Limitations	• Does not differentiate between active and latent TB
	• Variability in test interpretation
	• Requires two office visits
	• False positives resulting from either of the following:
	  • Prior BCG vaccination
	  • Exposure to nontuberculous mycobacteria
	• False negatives are possible in patients with any of the following:
	  • Sarcoidosis, Immunosuppressed state (anergy), Age < 6 months, Recent (within 8–10 weeks) or very old (many years) TB infection, Disseminated TB disease
		• No differentiation between active and latent TB
		• Expensive
		• Errors in collecting and transporting blood can decrease accuracy.

Vaccinations - Bacillus Calmette-Guérin vaccine (BCG)

- **Composition:** live attenuated strain of M. bovis
- It is a live freeze-dried vaccine which must be reconstituted
- Administered intra-dermally at the deltoid region on the left side
- should immunize infants and under 5 years with single dose of BCG
- **Contraindications**
  - Immunocompromised individuals
  - Pregnancy

Treatment

- Isoniazid
- Rifampin
- ethambutol
- pyrazinamide

Thank You