Tuberculosis (TB)

Topic Covered

- Introduction to TB
- Mycobacterium tuberculosis complex (MTBC)
- Structure of Mycobacterium
- Signs and symptoms
- Pathophysiology
- Diagnosis
- Treatment

Introduction

- Tuberculosis is one of the oldest known human diseases is still is one of the major causes of mortality, since two million people die each year from this malady.
- TB has many manifestations, affecting bone, the central nervous system, and many other organ systems, but it is primarily a pulmonary disease that is initiated by the deposition of Mycobacterium tuberculosis, contained in aerosol droplets, onto lung alveolar surfaces.

Introduction

- TB is an airborne disease caused by the bacterium Mycobacterium tuberculosis (M. tuberculosis, MTB).
- The Mycobacterium tuberculosis complex (MTBC) consists of closely related species that cause tuberculosis in both humans and animals.
- This illness, still today, remains to be one of the leading causes of morbidity and mortality throughout the world. Members of the genus Mycobacterium are characterized by a very complex cell wall envelope that is responsible for the remarkable low permeability of their cells as well as the characteristic differential staining procedure (known as Zhiel-Neelsen acid-fast stain), which specifically stains all members of the genera.

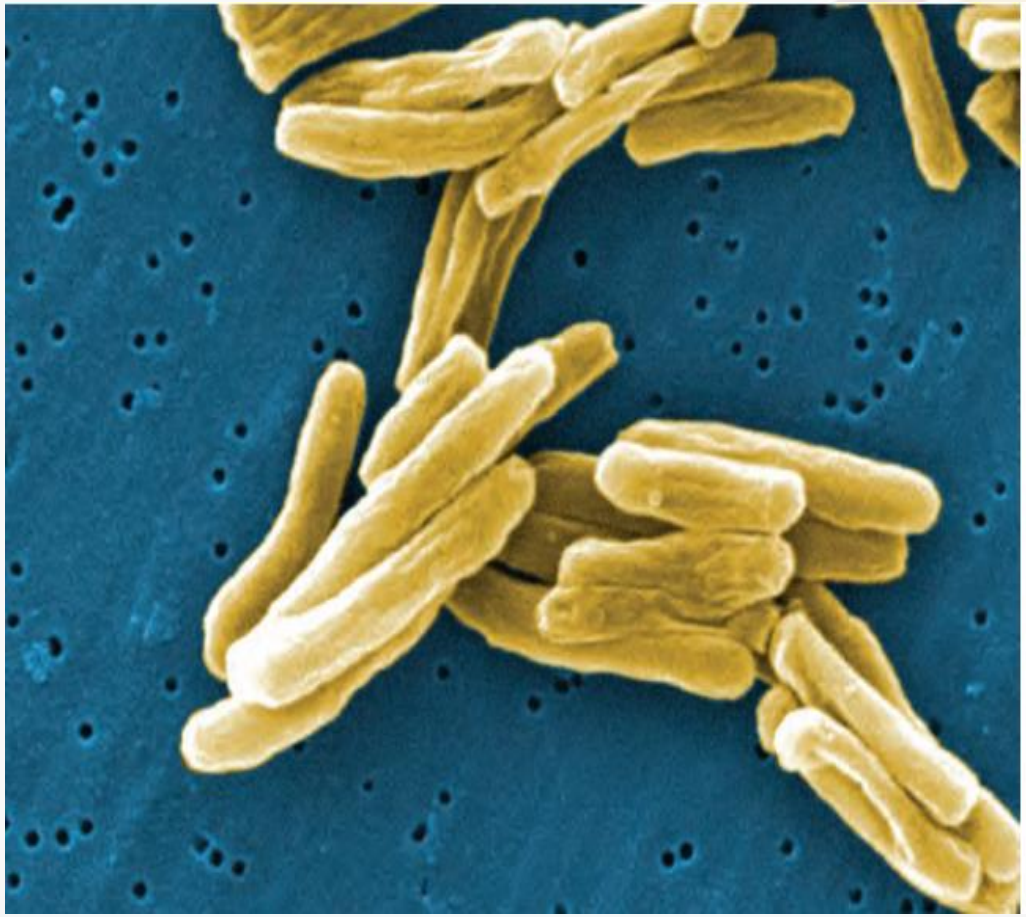
Mycobacterium tuberculosis complex (MTBC)

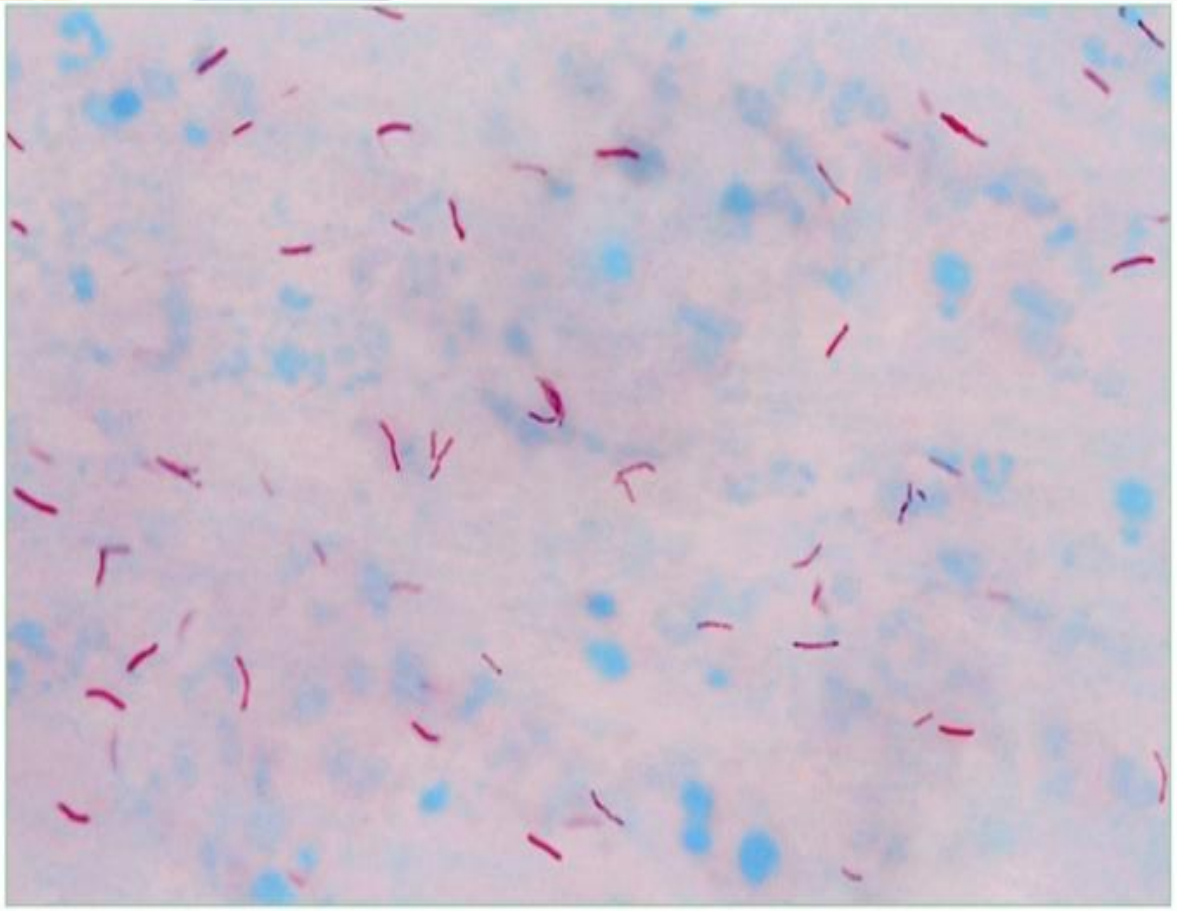
- The Mycobacterium tuberculosis complex (MTBC) refers to group of species (M. tuberculosis, Mycobacterium canettii, Mycobacterium africanum, Mycobacterium microti, M. bovis, Mycobacterium caprae and Mycobacterium pinnipedii) that are genetically very similar.
- Besides, a laboratory-selected mutant of M. bovis, isolated by Calmette and Guérin and known as M. bovis Bacille Calmette-Guérin (BCG), is the only vaccine used in TB prevention during early childhood.

Mycobacterium tuberculosis complex (MTBC)

Mycobacterium tuberculosis complex (MTBC)	Host
*M. **tuberculosis***	Human, Animals
*Mycobacterium **canettii***	Human
*Mycobacterium **africanum***	Human
*Mycobacterium **microti***	Rodents, immunocompromised Human
*M. **bovis***	Human, domestic or wild bovines and goats
*Mycobacterium **caprae***	Goats
*Mycobacterium **pinnipedii***	Seals

Mycobacteria- Structure





Mycobacteria- Structure

- Mycobacteria typically measure 0.5 µm by 3 µm, are classified as acid-fast bacilli, and have a unique cell wall structure crucial to their survival.
- The well-developed cell wall contains a considerable amount of a fatty acid, mycolic acid, covalently attached to the underlying peptidoglycan-bound polysaccharide arabinogalactan, providing an extraordinary lipid barrier.
- This barrier is responsible for many of the medically challenging physiological characteristics of tuberculosis, including resistance to antibiotics and host defense mechanisms. The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate.
- Another important component of the cell wall is lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism that is immunogenic and facilitates the survival of mycobacteria within macrophages.
- The cell wall is key to the survival of mycobacteria, and a more complete understanding of the biosynthetic pathways and gene functions and the development of antibiotics to prevent formation of the cell wall are areas of great interest.

Signs and symptoms

Signs and symptoms of active TB include:

- Coughing that lasts three or more weeks
- Coughing up blood
- Chest pain, or pain with breathing or coughing
- Unintentional weight loss
- Fatigue
- Fever
- Night sweats
- Chills
- Loss of appetite

Transmission

- Mycobacterium tuberculosis is **spread by small airborne droplets**, called droplet nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal tuberculosis.
- Introduction of M tuberculosis into the lungs leads to infection of the respiratory system; however, the organisms can spread to other organs, such as the lymphatics, pleura, bones/joints, or meninges, and cause extrapulmonary tuberculosis.

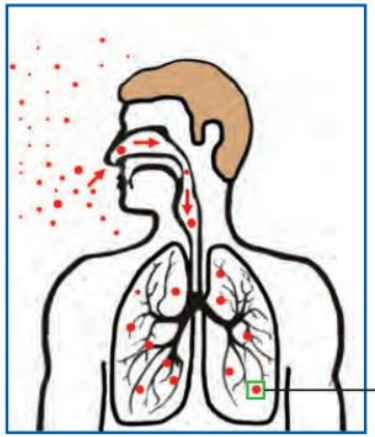
Pathophysiology

- Once inhaled, the infectious droplets settle throughout the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells exist.
- The mucus produced catches foreign substances, and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal. This system provides the body with an initial physical defense that prevents infection in most persons exposed to tuberculosis.
- Bacteria in droplets that bypass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages,the most abundant immune effector cells present in alveolar spaces.

Pathophysiology

- These macrophages, the next line of host defense, are part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection.
- Macrophages are readily available phagocytic cells that combat many pathogens without requiring previous exposure to the pathogens.
- Several mechanisms and macrophage receptors are involved in uptake of the mycobacteria. The mycobacterial lipoarabinomannan is a key ligand for a macrophage receptor. The complement system also plays a role in the phagocytosis of the bacteria.
- The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages. The subsequent phagocytosis by macrophages initiates a cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease, called primary progressive tuberculosis.

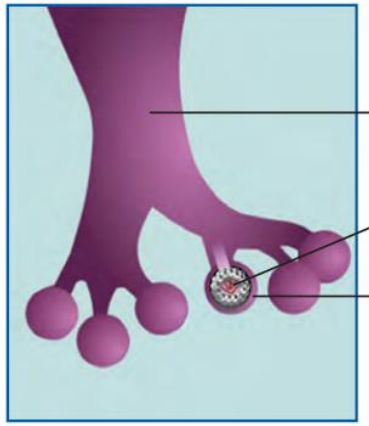
1.



Area of detail for boxes 2, 4, and 5

Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

2.



Bronchiole

Tubercle bacilli

Alveoli

Tubercle bacilli multiply in the alveoli.

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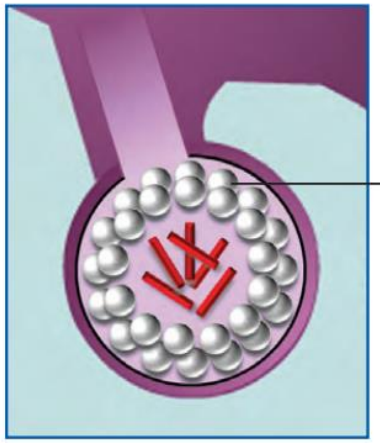

Special immune cells form a barrier shell (in this example, bacilli are in the lungs)

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)**.

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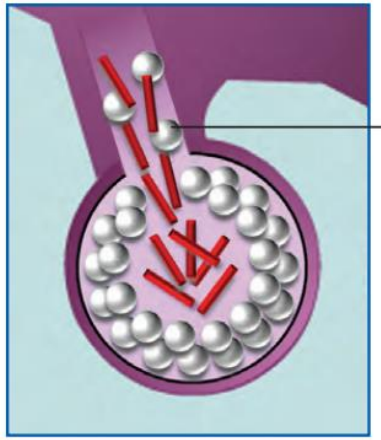


Shell breaks down and tubercle bacilli escape and multiply

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 (see diagram in box 3).

Differences in the Stages of TB

Early infection	Early primary progressive (active)	Late primary progressive (active)	Latent
Immune system fights infection Infection generally proceeds without signs or symptoms Patients may have fever, paratracheal lymphadenopathy, or dyspnea Infection may be only subclinical and may not advance to active disease	Immune system does not control initial infection Inflammation of tissues ensues Patients often have nonspecific signs or symptoms (eg, fatigue, weight loss, fever) Nonproductive cough develops Diagnosis can be difficult: findings on chest radiographs may be normal and sputum smears may be negative for mycobacteria	Cough becomes productive More signs and symptoms as disease progresses Patients experience progressive weight loss, rales, anemia Findings on chest radiograph are normal Diagnosis is via cultures of sputum	Mycobacteria persist in the body No signs or symptoms occur Patients do not feel sick Patients are susceptible to reactivation of disease Granulomatous lesions calcify and become fibrotic, become apparent on chest radiographs Infection can reappear when immunosuppression occurs

Latent Tuberculosis

- Persons with latent tuberculosis infection have M. tuberculosis in their bodies, but do not have TB disease and cannot spread the infection to other people.
- A person with LTBI is not regarded as having a case of TB. The process of LTBI begins when extracellular bacilli are ingested by macrophages and presented to other white blood cells.
- This triggers the immune response in which white blood cells kill or encapsulate most of the bacilli, leading to the formation of a granuloma.
- At this point, LTBI has been established. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.

Latent Tuberculosis

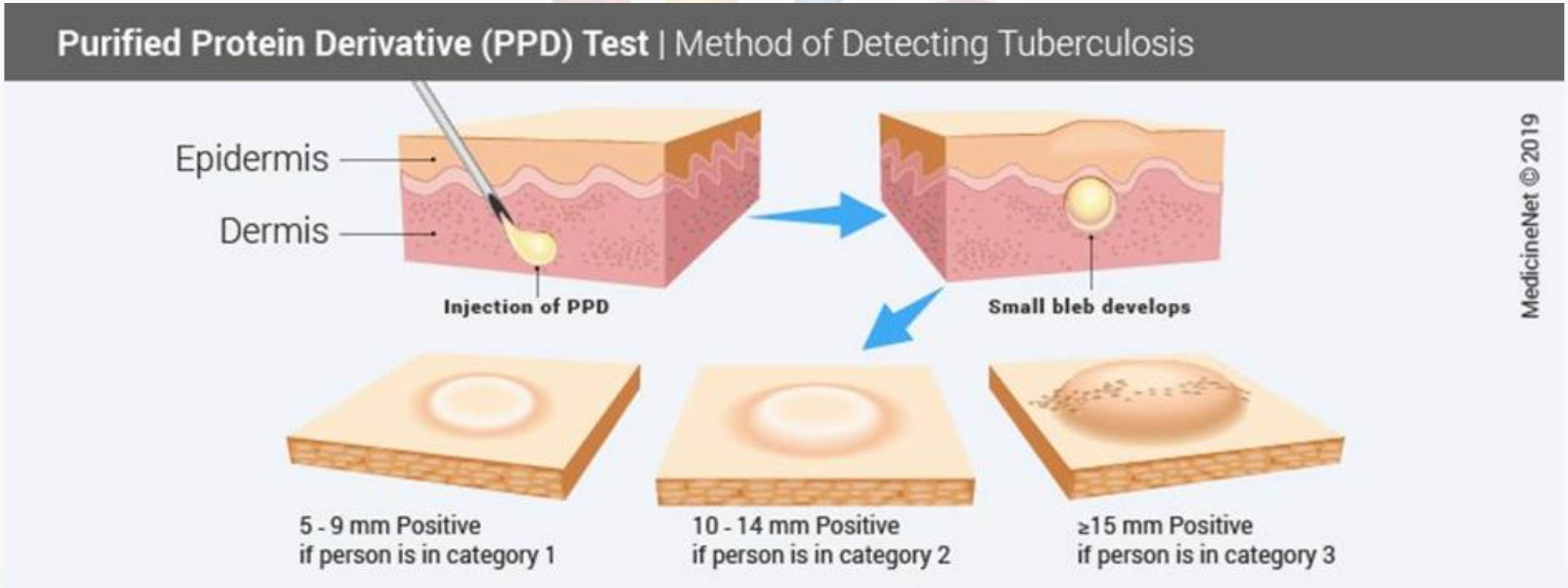
- Mycobacterium tuberculosis organisms can be enclosed, but are difficult to completely eliminate.
- Persons with latent tuberculosis have no signs or symptoms of the disease, do not feel sick, and are not infectious. However, viable bacilli can persist in the necrotic material for years or even a lifetime, and if the immune system later becomes compromised, as it does in many critically ill patients, the disease can be reactivated.
- Although coinfection with human immunodeficiency virus is the most notable cause for progression to active disease, other factors, such as uncontrolled diabetes mellitus, sepsis, renal failure, malnutrition, smoking, chemotherapy, organ transplantation, and long-term corticosteroid usage, that can trigger reactivation of a remote infection are more common in the critical care setting.

Primary Progressive Tuberculosis (ACTIVE TB)

- This condition makes you sick and in most cases can spread to others. It can occur in the first few weeks after infection with the TB bacteria, or it might occur years later.
- Active tuberculosis develops in only 5% to 10% of persons exposed to M tuberculosis. When a patient progresses to active tuberculosis, early signs and symptoms are often nonspecific.
- Manifestations often include progressive fatigue, malaise, weight loss, and a low-grade fever accompanied by chills and night sweats. Wasting, a classic feature of tuberculosis, is due to the lack of appetite and the altered metabolism associated with the inflammatory and immune responses.
- Wasting involves the loss of both fat and lean tissue; the decreased muscle mass contributes to the fatigue. The sputum may also be streaked with blood. Hematologic studies might reveal anemia, which is the cause of the weakness and fatigue.

Diagnosis

Tuberculosis skin test (Mantoux test)



Tuberculosis skin test (Mantoux test)

- The tuberculosis skin test determines if someone has developed an immune response to the bacterium that causes tuberculosis (TB).
- This response can occur if someone currently has TB, if they were exposed to it in the past, or if they received the BCG vaccine against TB. The tuberculin skin test is based on the fact that infection with M. tuberculosis bacterium produces a delayed-type hypersensitivity skin reaction to certain components of the bacterium.
- The standard recommended tuberculin test, known as the Mantoux test, is administered by injecting a 0.1 mL of a liquid containing 5 TU (tuberculin units) of PPD into the top layers of skin (intradermally, immediately under the surface of the skin) of the forearm. Doctors should read skin tests 48-72 hours after the injection.

Tuberculosis skin test (Mantoux test)

- Reaction in the skin to tuberculin PPD begins when specialized immune cells, called T cells, sensitized by prior infection, are attracted by the immune system to the skin site where they release chemical messengers called lymphokines.
- These lymphokines induce induration (a hard, raised area with clearly defined margins at and around the injection site) through local vasodilation (expansion of the diameter of blood vessels) leading to fluid deposition known as edema, fibrin deposition, and attraction of other types of inflammatory cells to the area.

Tuberculosis skin test (Mantoux test)

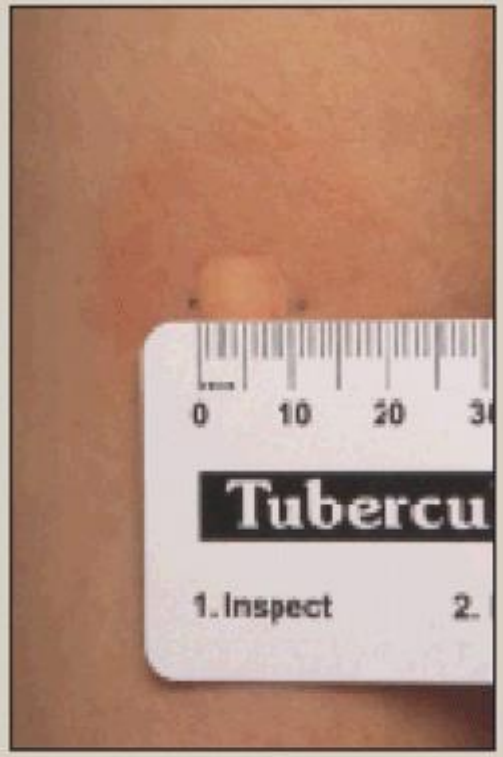


Image courtesy of Centers for Disease Control and Prevention.[34]

Diameter of induration	Considered positive for
≥5	Persons at high risk for tuberculosis: Patients with chronic diseases (eg, infection with human immunodeficiency virus) Persons with recent exposure to tuberculosis Patients with findings on radiographs suggestive of tuberculosis Employees of hospitals and long-term care facilities
≥10	Persons at risk for tuberculosis: Injectable drug users Persons in close living conditions Persons born in countries with high prevalence of tuberculosis
≥15	Persons who do not belong to either of the other groups

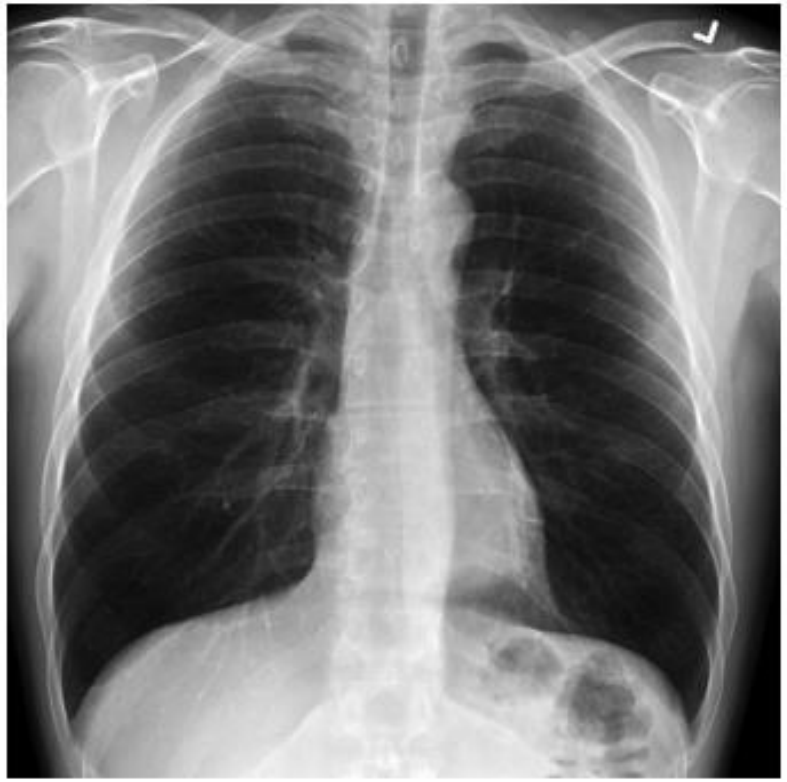
Tuberculosis skin test (Mantoux test)

- On the other hand, a negative test does not always mean that a person is free of tuberculosis.
- People who have been infected with TB may not have a positive skin test (known as a false negative result) if their immune function is compromised by chronic medical conditions, cancer chemotherapy, or AIDS.
- Additionally, 10%-25% of people with newly diagnosed tuberculosis of the lungs will also have a negative result, possibly due to poor immune function, poor nutrition, accompanying viral infection, or steroid therapy.

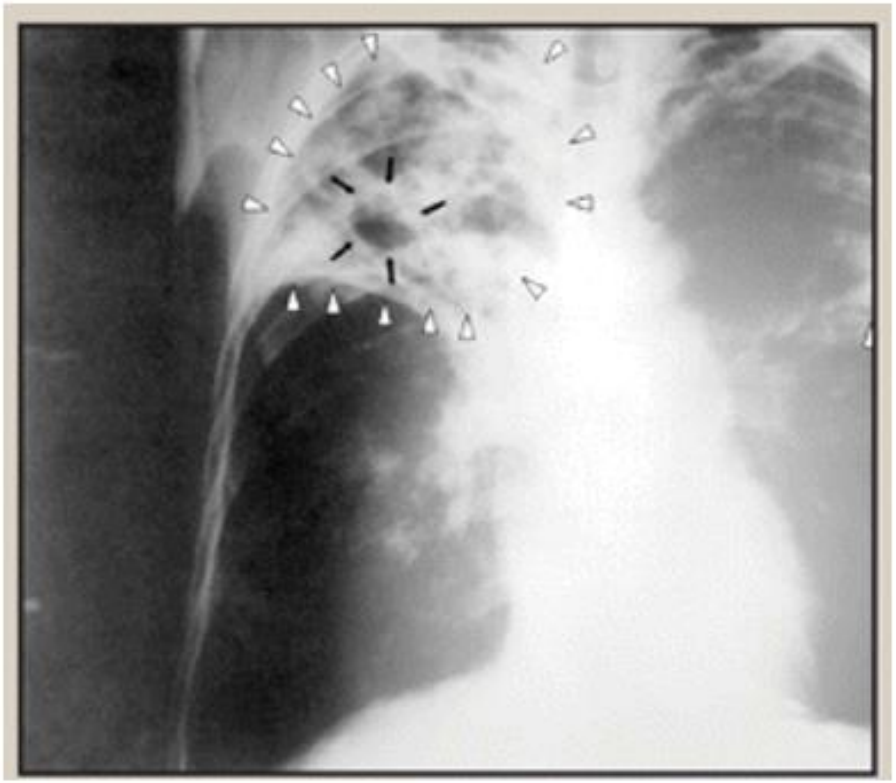
Imaging tests

- If you've had a positive skin test, your doctor is likely to order a chest X-ray or a CT scan.
- This may show white spots in your lungs where your immune system has walled off TB bacteria, or it may reveal changes in your lungs caused by active tuberculosis.
- CT scans provide more-detailed images than do X-rays.

Imaging tests



Normal Chest X Ray



Bilateral advanced pulmonary tuberculosis and cavitation in apical area of right lung.

Diagnosis

Sputum tests

- If your chest X-ray shows signs of tuberculosis, your doctor may take samples of your sputum — the mucus that comes up when you cough. The samples are tested for TB bacteria. Sputum samples can also be used to test for drug-resistant strains of TB. Because most mycobacteria grow slowly, 3 to 6 weeks may be required for detectable growth on solid media.

HPLC

- Used to isolate and differentiate cell wall mycolic acids provides confirmation of the disease in 4 to 14 days.

PCR

- Newer diagnostic techniques for faster detection of M tuberculosis include nucleic acid amplification tests. In these tests, molecular biology methods are used to amplify DNA and RNA, facilitating rapid detection of microorganisms; the tests have been approved by the Food and Drug Administration.

Treatment

- For active tuberculosis, you must take antibiotics for at least six to nine months. The exact drugs and length of treatment depend on your age, overall health, possible drug resistance and the infection's location in the body.

Most common TB drugs

- If you have latent tuberculosis, you may need to take only one or two types of TB drug. Active tuberculosis, particularly if it's a drug-resistant strain, will require several drugs at once. The most common medications used to treat tuberculosis include:
- Isoniazid
- Rifampin (Rifadin, Rimactane)
- Ethambutol (Myambutol)
- Pyrazinamide

Treatment

- If you have drug-resistant TB, a combination of antibiotics called fluoroquinolones and injectable medications, such as amikacin or capreomycin (Capastat), are generally used for 20 to 30 months.
- Some types of TB are developing resistance to these medications as well.
- Some drugs may be used as add-on therapy to the current drug-resistant combination treatment, including:
- Bedaquiline (Sirturo)
- Linezolid (Zyvox)

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