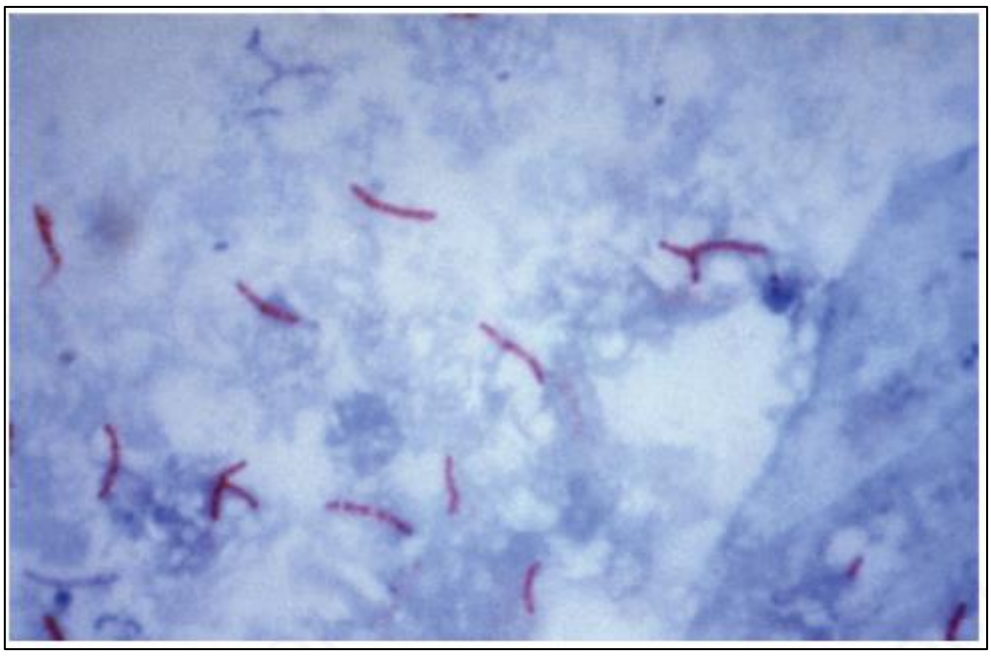
Mycobacteria

Mycobacteria are aerobic, acid-fast bacilli (rods). They are neither gram-positive nor gram-negative (i.e., they are stained poorly by the dyes used in Gram stain).

They are virtually the only bacteria that are acid-fast. The term acid-fast refers to an organism's ability to retain the carbolfuchsin stain despite subsequent treatment with an ethanol–hydrochloric acid mixture. The high lipid content (approximately 60%) of their cell wall makes mycobacteria acid-fast. The major pathogens are Mycobacterium tuberculosis, the cause of tuberculosis, and Mycobacterium leprae, the cause of leprosy. Atypical mycobacteria, such as Mycobacterium avium-intracellulare complex and Mycobacterium kansasii, can cause tuberculosis-like disease but are less frequent pathogens. Rapidly growing mycobacteria, such as Mycobacterium chelonae, occasionally cause human disease in immunocompromised patients or those in whom prosthetic devices have been implanted.



Mycobacterium tuberculosis

MYCOBACTERIUM TUBERCULOSIS

Disease

This organism causes tuberculosis. Worldwide, *M. tuberculosis* causes more deaths than any other single microbial agent. Approximately one-third of the world's population is infected with this organism. Each year, it is estimated that 1.7 million people die of tuberculosis and that 9 million new cases occur. An estimated 500,000 people are infected with a multidrug-resistant strain of M. tuberculosis.

Important Properties

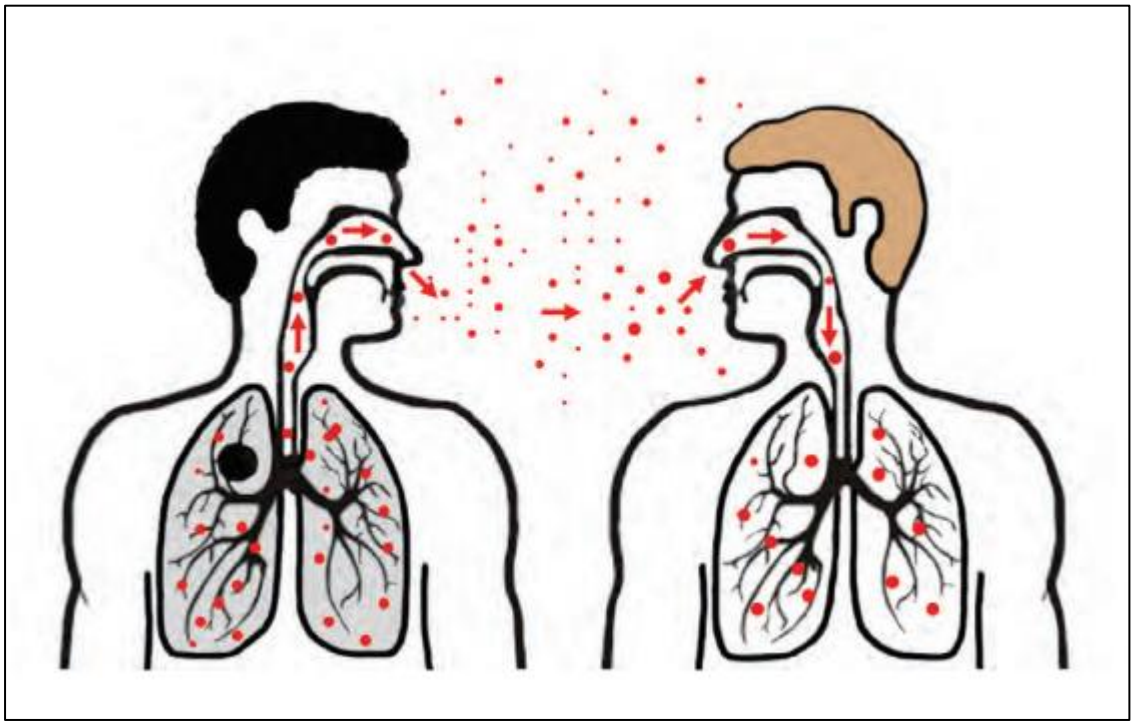
Mycobacterium tuberculosis grows slowly (i.e., it has a doubling time of 18 hours, in contrast to most bacteria, which can double in number in 1 hour or less). Because growth is so slow, cultures of clinical specimens must be held for 6 to 8 weeks before being recorded as negative. *Mycobacterium tuberculosis* can be cultured on bacteriologic media, whereas *M. leprae* cannot. Media used for its growth (e.g., Löwenstein-Jensen medium) contain complex nutrients (e.g., egg yolk) and dyes (e.g., malachite green). The dyes inhibit the unwanted normal flora present in sputum samples. *Mycobacterium tuberculosis* is an obligate aerobe; this explains its predilection for causing disease in highly oxygenated tissues such as the upper lobe of the lung and the kidney. The acid-fast property of *M. tuberculosis* (and other mycobacteria) is attributed to long-chain fatty acids called mycolic acids in the cell wall. Cord factor is correlated with virulence of the organism. The organism also contains several proteins, which, when combined with waxes, elicit delayed hypersensitivity. These proteins are the antigens in the purified protein derivative (PPD) skin test (also known as the tuberculin skin test). A lipid located in the bacterial cell wall called phthiocerol dimycocerosate is required for pathogenesis in the lung.

Mycobacterium tuberculosis is relatively resistant to acids and alkalis. NaOH is used to concentrate clinical specimens; it destroys unwanted bacteria, human cells, and mucus but not the organism. M. tuberculosis is resistant to dehydration and therefore survives in dried expectorated sputum; this property may be important in its transmission by aerosol. Strains of *M. tuberculosis* resistant to the main antimycobacterial drug, isoniazid (isonicotinic acid hydrazide, INH), as well as strains resistant to multiple antibiotics (called multidrug-resistant or MDR strains), have become a worldwide problem. This resistance is attributed to one or more chromosomal mutations, because no plasmids have been found in this organism. One of these mutations is in a gene for mycolic acid synthesis, and another is in a gene for catalase-peroxidase, an enzyme required to activate INH within the bacterium.

Transmission

Mycobacterium tuberculosis is transmitted from person to person by respiratory aerosols produced by coughing. The source of the organism is a cavity in the lung that has eroded into a bronchus. The portal of entry is the respiratory tract and the initial site of infection is the lung. In tissue, it resides chiefly within reticuloendothelial cells (e.g., macrophages). Macrophages kill most, but not all, of the infecting organisms. The ones that survive can continue to infect other adjacent cells or can disseminate to other organs. Humans are the natural reservoir of M. tuberculosis. Although some animals, such as cattle, can be infected, they are not the main reservoir for human infection. Most transmission occurs by aerosols generated by the coughing of "smear-positive" people (i.e., those whose sputum contains detectable bacilli in the acid-fast stain). However, about 20% of people are infected by aerosols produced by the coughing of "smear-negative" people. *Mycobacterium bovis* is found in cow's milk, which, unless pasteurized, can cause gastrointestinal tuberculosis in humans. most cases of tuberculosis are associated with reactivation in elderly, malnourished men. The risk of infection

and disease is highest among socioeconomically disadvantaged people, who have poor housing and poor nutrition. These factors, rather than genetic ones, probably account for the high rate of infection.



Pathogenesis

Infection occurs when a person inhales droplet nucleus containing tubercle bacilli that reach the alveoli of the lungs. These tubercle bacilli are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited. A small number may multiply intracellularly and are released when the macrophages die. If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain, and bone). This process of dissemination primes the immune system for a systemic response.

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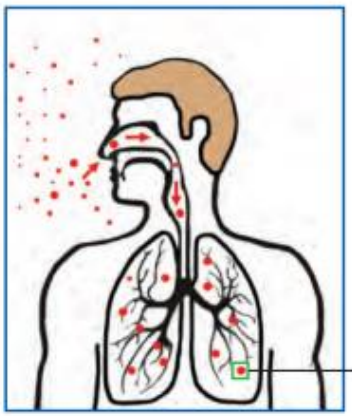
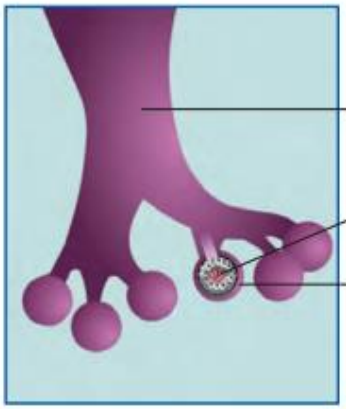


Area of detail for boxes 2, 4, and 5

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

2.



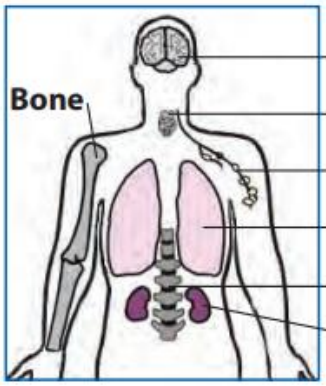
Bronchiole

Tubercle bacilli

Alveoli

Tubercle bacilli multiply in the alveoli.

3.



Brain

Larynx

Lymph node

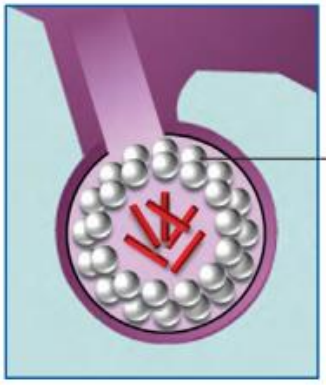
Lung

Spine

Kidney

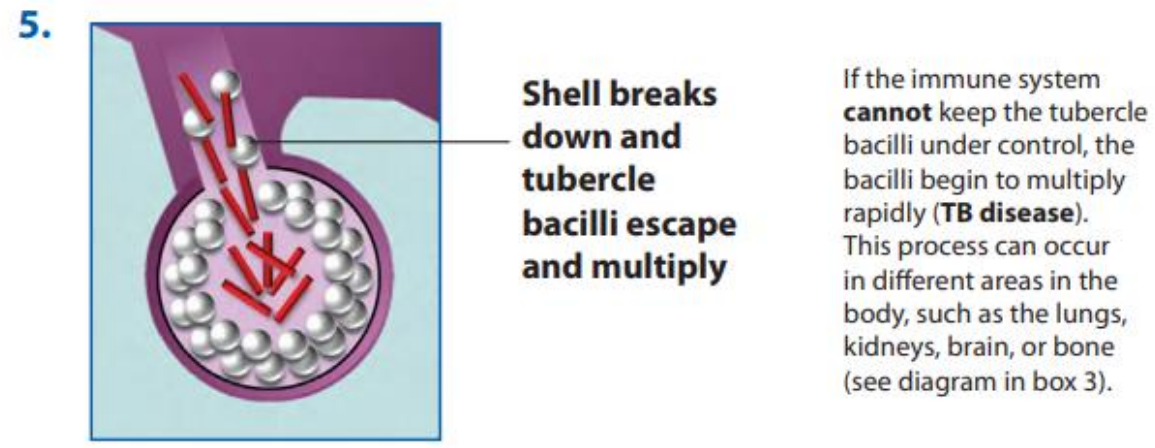
A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

4.



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)**.



Latent Tuberculosis Infection (LTBI)

Persons with LTBI 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. LTBI may be detected by using the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA). It can take 2 to 8 weeks after the initial TB infection for the body's immune system to be able to react to tuberculin and for the infection to be detected by the TST or IGRA. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.

Progression of TB

People who are exposed to *M. tuberculosis* may or may **not** develop LTBI.
People with LTBI may or may **not** develop TB disease.

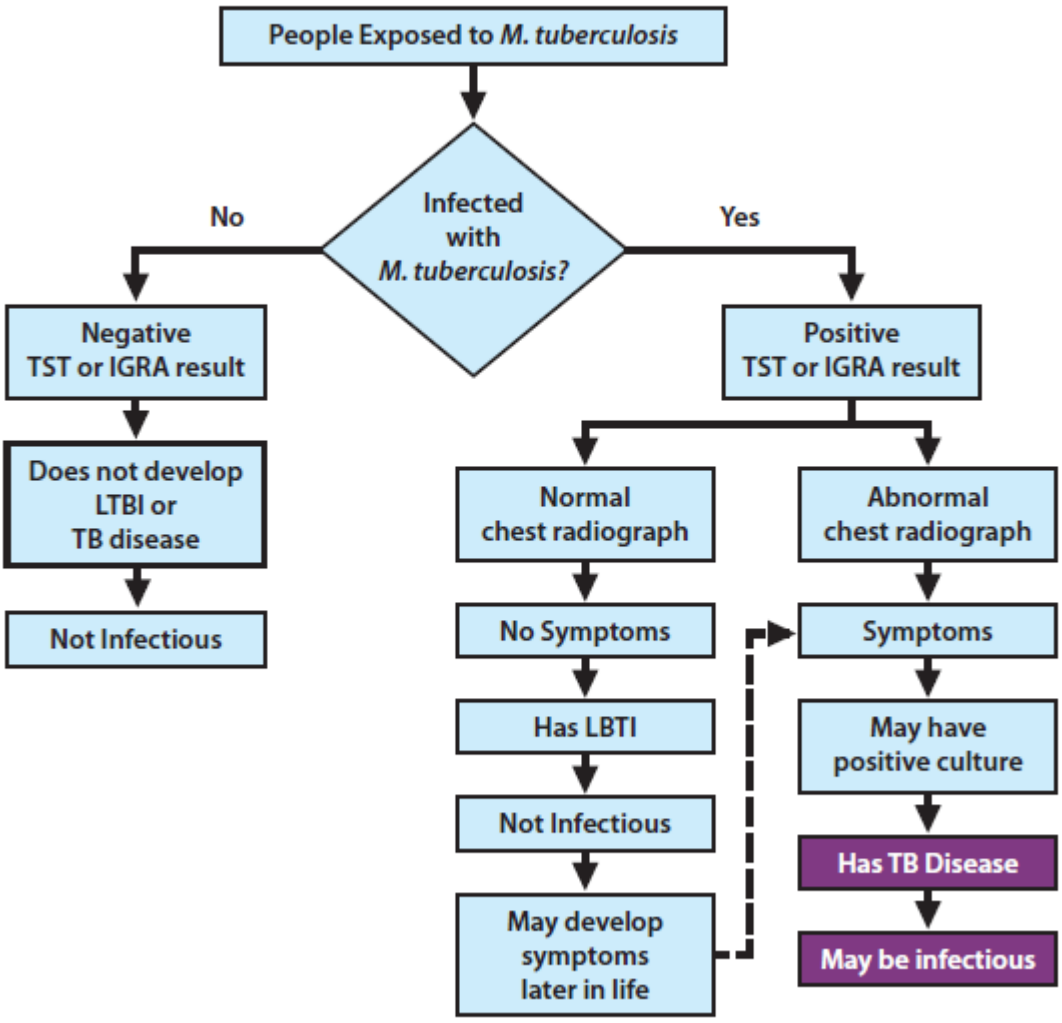


Table 2.5
LTBI vs. TB Disease

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

Sites of TB Disease

TB disease can occur in pulmonary and extrapulmonary sites.

Pulmonary

TB disease most commonly affects the lungs; this is referred to as pulmonary TB. Patients with pulmonary TB usually have a cough and an abnormal chest radiograph, and may be infectious. Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site or as disseminated disease.

Extrapulmonary

Extrapulmonary TB disease occurs in places other than the lungs, including the larynx, the lymph nodes, the pleura, the brain, the kidneys, or the bones and joints. In HIV-infected persons, extrapulmonary TB disease is often accompanied by pulmonary TB. Persons with extrapulmonary TB disease usually are not

infectious unless they have 1) pulmonary disease in addition to extrapulmonary disease; 2) extrapulmonary disease located in the oral cavity or the larynx; or 3) extrapulmonary disease that includes an open abscess or lesion in which the concentration of organisms is high, especially if drainage from the abscess or lesion is extensive, or if drainage fluid is aerosolized.

Miliary TB

Miliary TB occurs when tubercle bacilli enter the bloodstream and disseminate to all parts of the body, where they grow and cause disease in multiple sites. This condition is rare but serious. “Miliary” refers to the radiograph appearance of millet seeds scattered throughout the lung. It is most common in infants and children younger than 5 years of age, and in severely immunocompromised persons. Miliary TB may be detected in an individual organ, including the brain; in several organs; or throughout the whole body. The condition is characterized by a large amount of TB bacilli, although it may easily be missed, and is fatal if untreated. Up to 25% of patients with miliary TB may have meningeal involvement.

Central Nervous System

When TB occurs in the tissue surrounding the brain or spinal cord, it is called tuberculous meningitis. Tuberculous meningitis is often seen at the base of the brain on imaging studies. Symptoms include headache, decreased level of consciousness, and neck stiffness. The duration of illness before diagnosis is variable and relates in part to the presence or absence of other sites of involvement. In many cases, patients with meningitis have abnormalities on a chest radiograph consistent with old or current TB, and often have miliary TB.

Persons at Increased Risk for Progression of LTBI to TB Disease

1. Persons infected with HIV.
2. Children younger than 5 years of age.
3. Persons who were recently infected with M. tuberculosis (within the past 2 years).
4. Persons with a history of untreated or inadequately treated TB disease, including persons with fibrotic changes on chest radiograph consistent with prior TB disease.
5. Persons who are receiving immunosuppressive drug therapy following organ transplantation.
6. Persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, or cancer of the head, neck, or lung.
7. Persons who weigh less than 90% of their ideal body weight.
8. Cigarette smokers and persons who abuse drugs and/or alcohol.

Signs and symptoms of active TB include:

1. Coughing that lasts three or more weeks
2. Coughing up blood
3. Chest pain, or pain with breathing or coughing
4. Unintentional weight loss
5. Fatigue
6. Fever
7. Night sweats
8. Chills
9. Loss of appetite

Tuberculosis can also affect other parts of your body, including your kidneys, spine or brain. When TB occurs outside your lungs, signs and symptoms vary according to the organs involved. For example, tuberculosis of the spine may

give you back pain, and tuberculosis in your kidneys might cause blood in your urine.

Laboratory diagnosis

1. Acid fast staining of sputum (low sensitivity).
2. Culture on Lownestein- Jensen medium for up to 8 weeks.
3. Liquid BACTEC medium, radioactive metabolites are present, and grow can be detected by the production of radioactive carbon dioxidein about two weeks. (more rapid and reliable).
4. Nucleic acid amplification test (NAATs) ⟶ (sputum) this test is highly specific, but their sensitivity varies.
5. TB Skin test (TST).
6. Interferon- γ release assay (IGRA), blood cells from the patient are exposed to antigens from M. tuberculosis and the amount of interferon- γ released from the cells is measured. (highly sensitive and specific).

Note that IGRA and TST tests are positive in both latent and in active tuberculosis, so any person with a positive test must be evaluated for the prescence of active disease by obtaining the chest X-ray and sputum sample.

Treatment

Multidrug therapy is used to prevent the emergence of drug-resistant mutants during the long (6- to 9-month) duration of treatment. (Organisms that become resistant to one drug will be inhibited by the other.) Isoniazid (INH), a bactericidal drug, is the mainstay of treatment. Treatment for most patients with pulmonary tuberculosis is with three drugs: INH, rifampin, and pyrazinamide. INH and rifampin are given for 6 months, but pyrazinamide treatment is stopped after 2 months.

Prevention

BCG vaccine can be used to induce partial resistance to tuberculosis. The vaccine contains a strain of live, attenuated M. bovis called bacillus Calmette-Guérin. The vaccine is effective in preventing the appearance of tuberculosis as a clinical disease, especially in children.