Microbiology

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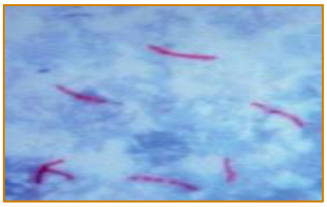
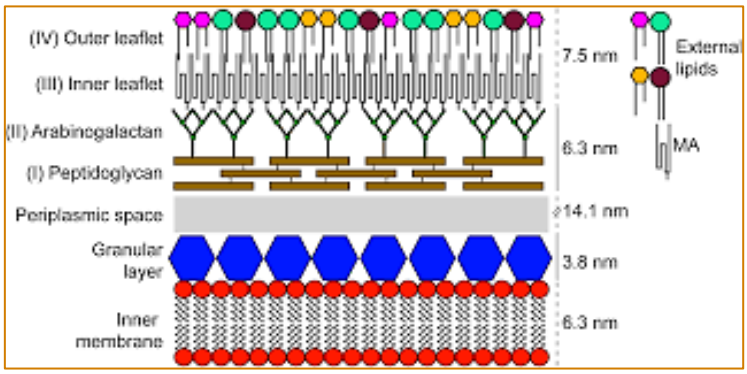
Mycobacteria

- **Overview of Mycobacteria**
  - ***General Characteristics:***
    - ✓ Mycobacteria are rod-shaped, aerobic, non-spore-forming bacteria.
    - ✓ They include Mycobacterium tuberculosis (Mtb), which causes tuberculosis (TB), Mycobacterium leprae (causing leprosy), and other non-tuberculous mycobacteria (NTM).
    - ✓ NTM, such as Mycobacterium avium complex (MAC), are opportunistic pathogens, particularly in immunocompromised individuals.

- **Mycobacterium Tuberculosis (Mtb)**
  - Discovery: Mtb was identified by Robert Koch in the 19th century using a special stain (ZN stain) to reveal the bacteria in patient sputum.
  - It includes *M. tuberculosis (Mtb), Mycobacterium africanum, Mycobacterium bovis, Mycobacterium microti, Mycobacterium caprae, Mycobacterium pinnipedii, Mycobacterium suricatte, Mycobacterium mungi, Mycobacterium dassie, Mycobacterium oryx and Mycobacterium canetti*
  - Morphology: Mtb are thin rods (~0.3–3 µm), acid-fast (resistant to decolorization by acid-alcohol), are obligate aerobes and derive energy from the oxidation of many simple carbon compounds and grow slowly with a doubling time of about 18 hours.



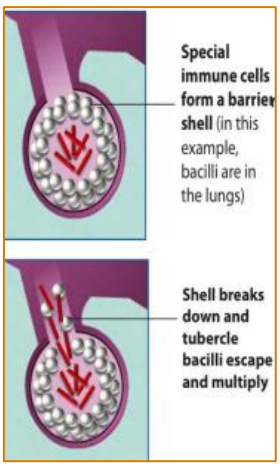
  - Cell Wall: The mycobacterial cell wall contains peptidoglycans, arabinogalactans, and mycolic acids. These components contribute to the bacteria's resistance to chemicals and its virulence.
    - ✓ The mycobacterial cell wall consists of an inner and outer layer surrounding the plasma membrane.
      - The inner compartment contains three macromolecules: peptidoglycans (PG), arabinogalactans (AG), and mycolic acids (MA), forming the MA-AG-PG complex.
    - ✓ The peptidoglycan layer surrounds the ***plasma membrane***, consisting of polymers of N-acetyl glucosamine and N-acetyl muramic acid (NAG-NAM) linked by peptide bridges.
    - ✓ Arabinans are mostly attached to long-chain mycolic acids, contributing to the thick, waxy lipid coat of mycobacteria, which increases impermeability and virulence.
    - ✓ Mycolic acids (C78–C90 fatty acids), waxes, and phosphatides make up 50% of the dry weight of the mycobacterial cell envelope.
    - ✓ Mycolic acids are esterified to glycerol and trehalose, forming trehalose dimycolates (TDM) (Cord Factor) and trehalose monomycolates (TMM).

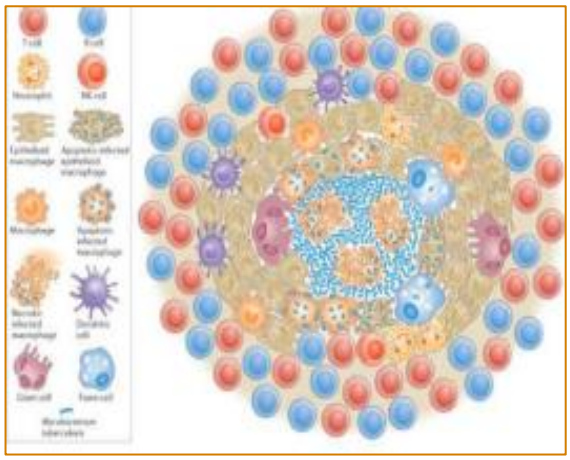


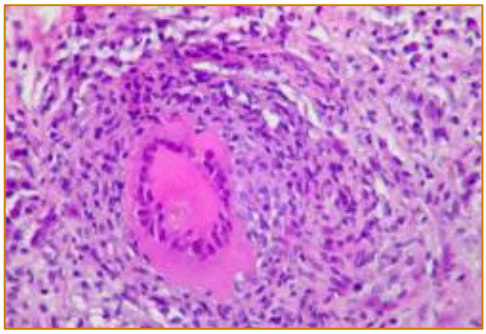
- **Epidemiology and Transmission of Tuberculosis**
  - Global Burden: A third of the world's population is infected with TB bacteria. However, not all will develop active TB.
    - ✓ There are ***two TB-related conditions:*** latent TB infection (LTBI) and active TB disease. If untreated, TB disease can be fatal. People with LTBI do not feel sick, have no symptoms, and cannot spread TB.
    - ✓ Approximately one-third of the global population is infected with TB bacteria, but it remains in a latent state.
    - ✓ TB can spread via the *lymphatic system* or through the *bloodstream* (hematogenous, also known as miliary TB).
  - Transmission: TB is airborne, primarily spread through coughing, sneezing, and speaking. It can also spread via unpasteurized milk and direct inoculation.
  - Extrapulmonary TB: TB can spread from the lungs to other parts of the body, including the lymph nodes, pericardium, kidneys, spine, and brain.

- **Pathogenesis and Clinical Manifestations**
  - Granuloma Formation: The immune system responds to TB infection by forming granulomas that can contain the bacteria (latent TB infection). If the immune response fails, TB disease develops.
    - ✓ Mycobacteria are transmitted through droplets when infected individuals cough, sneeze, or speak. These droplets evaporate, leaving bacteria small enough to be inhaled and reach the alveoli.
    - ✓ Inside the alveoli, the immune system releases cytokines and lymphokines, stimulating monocytes and macrophages.
    - ✓ Mycobacteria multiply within macrophages. Some macrophages become better at killing the bacteria, while others may be killed by the bacteria.
    - ✓ A granuloma, a barrier shell, forms to contain and control the bacilli, resulting in latent TB infection (LTBI).
    - ✓ If the immune system cannot control the bacilli, they multiply rapidly, leading to active TB disease.
    - ✓ Exudative type: An acute inflammatory reaction with edema fluid, polymorphonuclear leukocytes, and monocytes surrounds the bacilli, resembling bacterial pneumonia, especially in lung tissue.
    - ✓ Productive type: A chronic granuloma develops with three zones:

      1. A *central area* with multinucleated giant cells containing bacilli.
      2. A *mid-zone* with pale epithelioid cells, often radially arranged.
      3. A *peripheral zone* with fibroblasts, lymphocytes, and monocytes.







- **Primary Infection and Reactivation Types of Tuberculosis**
  - ✓ Acute exudative lesion develops and spreads quickly to the lymphatics and regional lymph nodes, with rapid healing of the exudative lesion in tissue.
  - ✓ In primary infections, involvement can occur in any part of the lung, but it is most often at the base.
  - ✓ The reactivation type is typically caused by tubercle bacilli that have survived in the primary lesion.
  - ✓ Reactivation almost always begins at the apex of the lung, where the oxygen tension (PO2) is highest.

- **Clinical Features:** Active pulmonary TB typically involves symptoms such as coughing, weight loss, fever, night sweats, and hemoptysis (coughing blood). The disease is chronic and often presents slowly, mimicking other diseases like cancer.
  - ✓ Classic symptoms of active pulmonary TB include coughing, *weight loss/anorexia, fever, night sweats, hemoptysis (coughing blood), dyspnea (chest pain), and malaise/fatigue*.
  - ✓ Tuberculosis typically presents as a chronic disease with slow progression, featuring weight loss, low-grade fever, and symptoms specific to the affected organ system. It can be mistaken for cancer due to its gradual onset.
  - ✓ TB is considered one of the great imitators, meaning it can resemble other diseases with similar symptoms.

- **Diagnostic Methods**
  - Smear Microscopy:
    - ✓ Ziehl-Neelsen staining or auramine staining is used to identify *acid-fast bacilli (AFB)* in suspected TB cases.
    - ✓ Three specimens from each patient should be examined microscopically for AFB, using *Ziehl-Neelsen* staining or demonstrating mycobacteria through *yellow fluorescence* after staining with *auramine.*
  - Culture: The most reliable method for diagnosing TB, using media include a nonselective medium and a selective medium
    - ✓ ***Liquid and solid mycobacterial cultures*** should be performed for every specimen, with recovered isolates identified using standard criteria such as Lowenstein-Jensen, Middlebrook 7H10, BACTEC radiometric system, and mycobacterial growth indicator tube (MGIT).
    - ✓ ***Culture for acid-fast bacilli*** is the most specific test for TB, enabling direct identification and determination of susceptibility of the causative organism.
  - Other Tests: Nucleic acid amplification tests (NAAT), Tuberculin skin tests (TST), and Interferon-gamma release assays (IGRAs) are also used.

- **Treatment and Prevention**
  - The course of TB treatment depends on whether the individual is in the latent or active stage, and on his or her probability of risk.
  - Drug Therapy: TB treatment typically involves a combination of drugs, such as isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and either ethambutol (EMB) or streptomycin (SM). The treatment course is usually divided into an intensive 2-month phase and a continuation phase lasting 4–6 months.
  - Prevention: Rapid diagnosis, isolation of infectious individuals, and vaccination (e.g., BCG vaccine) are key strategies. Isoniazid preventive therapy (IPT) is used for latent TB infection (LTBI).
    - ***Mycobacterium bovis Bacillus Calmette–Guérin (BCG),*** an attenuated vaccine derived from M. bovis, is the only licensed vaccine against tuberculosis (TB)

- **Non-Tuberculous Mycobacteria (NTM)**
  - NTM Characteristics:
    - Non-tuberculous mycobacteria (NTM) are environmental organisms, including both saprophytes and human pathogens.
    - NTM are classified into two groups: rapid growers (grow in <7 days) and slow growers, with further subdivision based on pigment production.
    - **Mycobacterium avium Complex (MAC or MAI)** is a notable group of NTM.
    - MAC infections rarely affect immunocompetent individuals but are common opportunistic infections in patients with AIDS.
  - Common NTM: Includes *Mycobacterium avium complex (MAC), M. kansasii, M. fortuitum complex, Mycobacterium chelonae-abscessus, Mycobacterium marinum and Mycobacterium ulcerans, Mycobacterium scrofulaceum.*

- **Mycobacterium Leprae**
  - Cause of Leprosy
  - M. leprae is an acid-fast bacterium that grows well at cooler body temperatures (e.g., skin and peripheral nerves).
  - The severity of the disease is dependent on the host's cell-mediated immune response to the bacilli (which live intracellular, like Mtb).
  - Types of Leprosy:
    1. Lepromatous leprosy (LL)
    2. Borderline lepromatous (BL)
    3. Tuberculoid leprosy (TL)
       - Are different forms, with symptoms involving skin lesions and sensory loss
       - The onset of leprosy is insidious.
       - The lesions involve the cooler tissue of the body, including the skin, superficial nerves, nose, pharynx, larynx, eyes, and testicles

  - Diagnosis: Diagnosed through skin or nasal mucosa biopsy of earlobe skin are smeared on a slide, stained with Ziehl-Neelsen for acid-fast bacilli, Biopsy of skin or of a thickened nerve gives a typical **histologic picture, No serologic tests are of value.**
  - Treatment: First-line therapy includes dapsone, rifampin, and clofazimine.
    - Sulfones such as dapsone are first-line therapy for both tuberculoid and lepromatous leprosy.
    - RMP or clofazimine generally is included in the initial treatment Regimens.

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