Tuberculosis

🌍 Epidemiology and Global Burden of TB

This section focuses on the global prevalence, incidence, and risk factors associated with Tuberculosis (TB). It highlights the disease's impact and the populations most affected.

1: TB Epidemiology Overview

Epidemiology: The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems.

1: Global Incidence and Prevalence

Global Burden: TB remains a major global health problem, with millions of new cases annually. *Incidence*: The rate of new cases of TB in a given population over a specific period. *Prevalence*: The total number of existing cases of TB in a population at a specific point in time. *Estimated 1.6 Billion Infected*: Approximately one-quarter of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (MTB). *Active TB Cases*: Around 10.6 million people worldwide have active TB disease, manifesting respiratory symptoms. *Childhood TB*: About 10% of active TB cases occur in children.

2: Mortality and Impact

Leading Cause of Death: TB is a significant cause of death globally, especially among those co-infected with HIV. *Mortality Rates*: High in certain regions, especially in those with limited access to healthcare and in individuals with HIV. *Co-infection with HIV*: Increases the risk of TB activation and mortality significantly. *Mortality Worldwide*: 6 million people die every year from causes related to or including TB.

3: High-Burden Countries

Endemic Regions: TB is highly prevalent in certain countries. *Key Countries*: India, China, Indonesia, Nigeria, and South Africa account for a significant proportion of global TB cases. *Geographic Distribution*: Incidence varies greatly, with Sub-Saharan Africa and South Asia having the highest rates. *Risk Factors*: include migration from high-prevalence countries, age (above 65), and socioeconomic factors.

2: Risk Factors and Vulnerable Populations

1: HIV and TB Co-Infection

Strong Correlation: There is a strict correlation between HIV and TB, as HIV increases the risk of TB reactivation. *Immunosuppression*: HIV weakens the immune system, increasing susceptibility to TB. *Treatment Challenges*: Co-infection complicates treatment and increases mortality. *Testing for HIV*: Essential in TB patients, especially in high-prevalence areas. *Example*: Over 50% of TB patients in South Africa have HIV.

2: Other Immunosuppressive Factors

Immunosuppression: Any factor that reduces immune function can lead to TB reactivation. *Vitamin D Deficiency*: Low levels of vitamin D correlate with a higher risk of tuberculosis, as vitamin D controls T-cell responses. *Age*: The elderly are at higher risk due to age-related immune decline. *COVID-19 Impact*: The COVID-19 pandemic resulted in reduced TB notifications and higher mortality.

3: Environmental and Socioeconomic Factors

Sunlight and TB: Areas with less sunlight have higher TB incidence, correlating with vitamin D levels. *Crowded Living Conditions*: Increase TB transmission risk. *Migration*: Migrants from high-prevalence countries are at increased risk, particularly in the first years after migration.

3: Trends and Historical Data

Incidence Trends: The global incidence of TB is falling by approximately 2% annually. *Europe*: Incidence is relatively low, but Eastern Europe has the highest numbers in the region. *Italy*: Low incidence country, but with prevalence in young migrants and individuals over 65. *Impact of COVID-19*: Reduction in TB notification rates in some countries. *Reduction in TB Deaths*: The "End TB Strategy" aimed for a 35% reduction in TB deaths between 2015 and 2020.

🦠 Microbiology and Transmission

This section focuses on the microbiological aspects of *Mycobacterium tuberculosis* and how the disease is transmitted.

1: Microbiology of *Mycobacterium tuberculosis*

Mycobacterium tuberculosis (MTB): The causative agent of tuberculosis.

1: MTB Complex

MTB Complex: A group of closely related mycobacteria. *Species*: Includes *M. tuberculosis, M. bovis, M. africanum, M. canetti*, and others. *M. bovis*: Primarily transmitted through contact with infected cows or ingestion of contaminated dairy products. *Intestinal TB*: Often caused by *M. bovis* due to ingestion of contaminated milk products.

2: Bacterial Characteristics

Rod-Shaped Bacillus: *M. tuberculosis* is a rod-shaped bacterium. *Non-Motile*: It does not move independently. *Non-Sporogenous*: Does not form spores. *Aerobic*: Requires oxygen for survival and replication. *Intracellular Survival*: Can survive and replicate within macrophages. *Long Replication Cycle*: Slow growth results in a long replication cycle, requiring 30-70 days for culture.

3: Cell Wall Composition

Complex Cell Wall: The cell wall of *M. tuberculosis* is complex and waxy. *Mycolic Acid*: Contains mycolic acid, providing resistance to the immune system. *LAM Detection*: The presence of lipoarabinomannan (LAM) can be detected in tests.

2: Modes of Transmission

Airborne Transmission: TB is primarily transmitted through the air. *Droplet Nuclei*: Transmission occurs through airborne particles.

1: Airborne Particle Characteristics

Big Droplets: Can travel up to 1 meter. (e.g. meningitis from *Neisseria*) *Small Droplets*: Can travel up to 3 meters (e.g. TB). *Infectious Droplets*: Can be viruses (e.g. influenza) affecting anyone in the room. *Particle Weight*: Airborne transmission depends on the weight of the particles.

2: Environmental Factors in Transmission

Environment Matters: Transmission rates are higher in crowded and poorly ventilated spaces. *High-Risk Conditions*: Include small rooms, lack of fresh air and sunlight. *Migration Context*: Migrants in the first few years often live in conditions increasing transmission.

🛡️ Pathogenesis and Immune Response

This section describes the progression of tuberculosis from infection to disease, focusing on the immune responses involved.

1: Initial Infection and Phagocytosis

Inhalation of Droplet Nuclei: TB infection begins with the inhalation of droplet nuclei containing *M. tuberculosis*. *Ciliary System*: The ciliary system in the respiratory tract typically expels the majority (90%) of inhaled droplet nuclei. *Alveolar Spaces*: The smallest particles (<2 µm) reach the distal alveolar spaces. *Macrophages*: The primary cells involved in the initial response. *Phagocytosis*: Mycobacteria are engulfed by alveolar macrophages.

1: Macrophage Response

Lysosomes and ROS: Macrophages attempt to eliminate the bacteria using lysosomes and reactive oxygen species. *Chemokine Production*: If macrophages cannot eliminate the bacteria, they produce chemokines. *Recruitment of Cells*: These chemokines attract other immune cells, particularly other macrophages.

2: Granuloma Formation and Structure

Granuloma Formation: Recruitment of immune cells leads to granuloma formation. *Granuloma*: A structure that walls off the bacteria, preventing further spread. *Caseous Necrosis*: The central region of a TB granuloma undergoes caseous necrosis. *Caseous Necrosis Description*: Macrophages, inflammatory cells, and bacteria are deprived of oxygen. *Unique to TB*: Caseous necrosis is a hallmark of TB granulomas, differentiating them from those formed in other diseases.

1: Granuloma Layers

Intermediate Stratum: Macrophages and monocytes. *External Stratum*: Epithelioid and giant multinucleated cells. *Central Zone*: Caseous Necrosis.

2: Stability and Reactivation

Dynamic Structure: The granuloma wall is constantly remodeled. *Immune Depression*: The process is sensitive to immune depression (e.g., HIV, corticosteroids). *Secondary TB*: Immune suppression allows mycobacteria to replicate, leading to secondary TB. *Before Immunosuppressants*: Patients must be tested for HIV, TB, and syphilis. *Reactivation Risk*: High if the immune system cannot maintain the granuloma.

3: Immune Response Outcomes

Effective Response: In the majority of infected individuals, the macrophages effectively contain the bacteria, forming a granuloma, resulting in latent TB. *Weak Response*: In 5-10% of infected individuals, the macrophage

response is weak. *Immunosuppressed Groups*: Immunosuppressed individuals and children under 5 years are more likely to have a weak response. *Primary TB*: The bacteria spreads throughout the body. *Extrapulmonary Manifestations*: Primary TB is associated with high amounts of extrapulmonary manifestations (e.g., TB meningitis). *BCG Vaccine*: Prevents primary tuberculosis but does not prevent secondary tuberculosis.

🩺 Clinical Presentation of Tuberculosis

This section covers the clinical manifestations of both pulmonary and extrapulmonary TB.

1: Pulmonary Tuberculosis

Classical Presentation: Pulmonary TB often has an insidious onset and a chronic course. *Chest Symptoms*: Cough (often productive), hemoptysis (late), and chest pain (usually pleuritic). *Non-Specific Symptoms*: Nonspecific constitutional symptoms are more common in children and HIV patients. *Extrapulmonary Symptoms*: May occur if the infection spreads beyond the lungs.

1: Symptom Onset and Progression

Subacute Onset: Symptoms develop gradually. *Chronic Nature*: Often characterized by a prolonged illness. *Delayed Diagnosis*: The diagnosis in individuals born in Italy is delayed more often than in those born abroad, due to the chronic and subacute onset.

2: Common Symptoms

Fever: Present in 65-80% of cases. *Chills/Night Sweats*: Common symptoms. *Fatigue/Malaise*: Frequently reported. *Anorexia/Weight Loss*: Typical signs. *Asymptomatic Cases*: 10-20% of TB cases may be asymptomatic at the time of diagnosis.

3: Radiological Findings

Varied Presentation: The appearance of TB on X-rays can vary. *Buddy Tree or Consolidation*: X-rays may show a "buddy tree" pattern, resembling bacterial pneumonia. *Cavitation*: Cavities may be present, indicating advanced disease. *Differential Diagnosis for Cavitation*: NTM, fungi, cancer, or pulmonary vasculitis. *Cavitation and Hemoptysis*: Association with advanced stages.

2: Extrapulmonary Tuberculosis

Extrapulmonary Disease: TB can affect any organ or tissue outside of the lungs.

1: Miliary Tuberculosis

Disseminated TB: A severe form of TB, similar to sepsis. *Spread*: The infection spreads widely through the lungs, blood, and lymph nodes. *Reticulonodular Pattern*: Characterized by numerous small nodules spread throughout the lungs. *Emergency Condition*: Requires immediate medical attention. *Contagious*: Patients are highly contagious.

2: TB Lymphadenitis

Lymph Node Involvement: Primarily affects children. *Location*: Commonly infraclavicular, cervical, or submandibular. *Unilateral vs. Bilateral*: Usually unilateral; bilateral involvement suggests systemic disease. *Lymph Node Characteristics*: Soft, non-painful, and cold. *Abscess and Bacterial Lymphadenoma*: Warm lymph nodes, indicating inflammation. *Diagnosis*: Biopsies, cultivation, and detection of TB in lymph nodes. *Prognosis*: Generally considered a benign form with low mortality.

3: TB Serositis

Serosal Involvement: Serous membranes (pericardium, peritoneum, pleura) can be affected. *Pleuritis*: The most common form of serositis due to its association with the lungs. *Complications*: Pericarditis has serious complications. *Unexplained Serositis*: Always consider TB. *Diagnosis*: Cultivation of serosal fluid to detect TB.

4: Other Extrapulmonary Sites

Laryngeal TB: Highly contagious. *Skin TB*: Can present with lesions, requiring biopsy for diagnosis. *CNS TB*: Includes TB meningitis, associated with the highest mortality rate. *TB Meningitis Symptoms*: Slow onset with weight loss and cranial nerve paralysis. *Hydrocephalus*: Common due to altered CSF circulation. *CSF Findings*: Clear CSF with lymphocytes, elevated proteins, and low glucose. *Tuberculomas*: Can cause CNS symptoms, identified via CT scan or MRI. *Spine TB*: Usually in the thoracic spine; Pott's disease is more common in the lumbar part. *Genitourinary TB*: Can affect the genital and urinary tracts.

🛡️ Immune Reconstitution Inflammatory Syndrome (IRIS)

This section details the Immune Reconstitution Inflammatory Syndrome (IRIS) associated with TB.

1: Definition and Mechanism

IRIS: An inflammatory response that occurs after the initiation of antiretroviral therapy (ART). *Paradoxical Reaction*: Paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started ART and have undergone reconstitution of their immune responses against this antigen. *HIV Treatment*: Occurs in patients with HIV who start antiretroviral therapy (ART). *Immune System Recovery*: The immune system is restored after ART. *Inflammatory Reaction*: The restored immune system overreacts to the mycobacteria.

1: Pathogenesis

Increased Lymphoproliferative Response: Increased response to *Mycobacterium* antigens in vitro. *Cutaneous Response*: Restoration of the cutaneous response to tuberculin. *Increased [IL-6]*: Increased levels of interleukin-6 and activation markers. *Genetic Associations*: Associated with certain genetic markers (e.g., TNFA-308*1, IL6-174G*).

2: Clinical Manifestations and Examples

Clinical Worsening: Patients experience a worsening of their condition after ART initiation. *Torino Case 2 Example*: Case of a patient with low CD4 cell count, initially sputum-negative for TB. *Treatment and Response*: Treatment of immunosuppression, which led to an inflammatory reaction after the immune system recovered. *IRIS Forms*: "Unmasking IRIS" and "Worsening IRIS".

3: Management of IRIS

Unmasking IRIS: Presents before ART. Requires diagnosis and treatment of the opportunistic infection. *Worsening IRIS*: Requires managing the infection. *NSAIDs*: May be used for mild cases. *Corticosteroids*: Prednisone (1 mg/kg) can be used. *ART Considerations*: Interruption of ART in case of life-threatening or serious disorders. *Monitor CD4 and Viral Load*: Monitoring CD4 counts and viral load to assess response and manage treatment.

🧪 Diagnosis and Treatment of TB

This section addresses the diagnostic methods and therapeutic approaches to tuberculosis.

1: Diagnostic Approaches

Active and Latent TB: Distinguishing between active and latent TB is crucial. *Active TB*: Diagnosing active tuberculosis requires identifying the

presence of the bacteria. *Latent TB*: Requires detecting evidence of prior infection.

1: Active TB Diagnosis

Sampling Methods: Sputum, serum, or urine samples can be used. *Culture*: The gold standard in microbiology, results available within 14-15 days. *Staining*: Ziehl-Neelsen staining can quickly identify TB bacteria under a microscope. *PCR*: Polymerase chain reaction (PCR) is a rapid method.

2: Latent TB Diagnosis

Purposes: Testing to identify latent infections in migrants or immunosuppressed individuals. *Mantoux Test*: Intradermal injection of a protein from *M. tuberculosis*; measured by papule size. *Positive Result*: A papule >1 cm is considered positive. *Limitations*: False positives due to BCG vaccination. *Interferon-Gamma Release Assays (IGRAs)*: Also known as QuantiFERON, measures interferon-gamma production in response to TB antigens. *Specificity*: IGRAs are more specific. *Sensitivity*: T cells react to TB antigens with very high sensitivity.

3: Test Comparisons

Feature Mantoux Test (TST) Interferon-Gamma Release Assays (IGRA) (e.g., QuantiFERON) Type In vivo In vitro Specificity Less specific More specific PPD PPD Boosting Specific antigens Patient Visits 2 1 Variability Inter-reader Lab variability Results 2-3 days 1 day Phlebotomy No Required Positive Control No Yes (+ control)

2: Treatment of Latent TB

Latent TB Treatment: Not always required, as the risk of reactivation is low. *Risk of Reactivation*: 5-10% chance of reactivation. *Indications for Treatment*: Certain groups are treated to prevent progression. *Treatment Regimen*: Isoniazid for 6 months (with vitamin B6 for pregnant women), or rifampin for 4 months.

1: High-Risk Groups for Latent TB Treatment

People Living with HIV (PLWH) Recent Contacts of TB Cases: Individuals exposed to TB. *Fibrotic Changes on Chest X-ray*: Showing old TB. *Organ Transplant Recipients*. *Immunosuppressed Individuals*: Taking high-dose corticosteroids or TNF-α antagonists. *High-Prevalence Countries*: Individuals from these regions. *Injection Drug Users*. *High-Risk Congregate Settings*:

Correctional facilities, nursing homes, etc. *Mycobacteriology Laboratory Personnel*. *Children under 4 Years or Exposed to High-Risk Adults*.

3: Active TB Treatment

Multidrug Therapy: The use of multiple drugs simultaneously. *Drug Resistance*: Due to the heterogeneous nature of the bacterial population. *Drug Choice Rationale*: Isoniazid for rapidly growing bacteria, Pyrazinamide for slowly growing bacteria, and Rifampicin for sporadically growing bacteria.

1: Treatment Regimen

Initial Phase: Four drugs: Rifampicin, Pyrazinamide, Ethambutol, and Isoniazid for 2 months. *Continuation Phase*: Rifampicin and Isoniazid for 4 months. *Contagiousness Reduction*: After 2 weeks of treatment, contagiousness is approximately 5%. *Duration of Therapy*: Additional months may be required for TB meningitis or bone disease.

2: Drug Doses and Side Effects

Common TB Drugs: Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide. *Rifampicin (10 mg/kg)*: Orange urine and other body fluids, hepatotoxicity, CYP and PgP induction, and drug interactions. *Isoniazid + Pyridoxine (5 mg/kg)*: Hepatotoxicity, peripheral neuropathy. *Ethambutol (15-20 mg/kg)*: Uveitis, color blindness. *Pyrazinamide (20-25 mg/kg)*: Hepatotoxicity, hyperuricemia. *Ethambutol Note*: Reversible side effect with early detection, but can be irreversible in some patients. *Isoniazid + B6*: Essential to prevent peripheral neuropathy. *Efficacy:* The efficacy of the 4 drug regimen is usually 95% but the true efficacy is around 85% due to factors such as adherence, side effects, etc. *HIV patients*: HIV patients have a real efficacy of 75%. *MDR-TB efficacy*: MDR-TB has an efficacy of 50%.

4: Drug-Resistant TB

MDR-TB (Multi-Drug Resistant TB): Resistant to isoniazid and rifampicin. *Global Prevalence*: Affects 3.1% of new cases and 18% of previously treated cases. *XDR-TB (Extensively Drug-Resistant TB)*: Resistant to fluoroquinolones and a group A drug (bedaquiline or linezolid). *Treatment for Resistant Strains (Past)*: 5 to 6 drugs for 2 years. *New Guidelines for Resistant Strains*: 3-4 drugs for 6 months (bedaquiline, pretomanid, linezolid, and moxifloxacin)

💡 Important Facts to Memorize

- **Global Burden:** TB is a leading cause of death worldwide, with approximately 10.6 million active cases annually.
- **HIV and TB:** HIV significantly increases the risk of TB reactivation and mortality, often coexisting.
- **Transmission:** Primarily airborne, influenced by droplet nuclei and environmental factors such as crowding and ventilation.
- **Pathogenesis:** Granuloma formation is key, with caseous necrosis in the center, which can be compromised by immune deficiencies, leading to reactivation.
- **Clinical Presentation: Pulmonary TB:** Insidious onset, with cough, hemoptysis, and potential for cavitation.
- **Clinical Presentation: Extrapulmonary TB:** Miliary TB is a severe disseminated form. TB lymphadenitis involves cold, non-painful lymph nodes.
- **IRIS:** Immune Reconstitution Inflammatory Syndrome occurs after ART initiation in HIV patients, worsening the condition.
- **Diagnosis: Active TB:** Relies on sputum, serum, or urine samples; culture and PCR are gold standards.
- **Diagnosis: Latent TB:** Diagnosed with Mantoux test or IGRA, like QuantiFERON.
- **Latent TB Treatment:** Recommended for high-risk groups (HIV, recent contacts) with Isoniazid or Rifampin.
- **Active TB Treatment:** Uses a 6-month, four-drug regimen: Rifampicin, Pyrazinamide, Ethambutol, and Isoniazid.
- **Drug Side Effects:** Be aware of Rifampicin (orange urine, hepatotoxicity), Isoniazid (peripheral neuropathy), Ethambutol (visual disturbances), and Pyrazinamide (hepatotoxicity, hyperuricemia).
- **MDR-TB:** Resistant to isoniazid and rifampicin.
- **XDR-TB:** Extremely resistant; requires newer, shorter treatment regimens.
- **Risk Factors for reactivation:** Immunosuppression from any cause (including HIV, steroids, etc.) and Vitamin D deficiency.

- **BCG Vaccine:** Prevents primary tuberculosis but not secondary tuberculosis.