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Review on Tuberculosis and its Treatment

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Abstract: *Tuberculosis (TB) is a life-threatening infectious disease caused by Mycobacterium tuberculosis, primarily affecting the lungs and manifesting through symptoms such as severe coughing, fever, and chest pain. Recent research efforts have yielded significant insights into the transmission, detection, and treatment of tuberculosis. The disease poses a considerable challenge to public health, ranking second in mortality rates following HIV/AIDS. The World Health Organization (WHO) collaborates with nations, partners, and civil society organizations to enhance the global response to TB. This review article aims to examine the epidemiology, diagnosis, symptoms, and treatment of TB, while also providing an overview of its current epidemiological trends, pathogenesis, immune response, and effective management strategies. Interferon-gamma release assays serve as whole blood tests for TB diagnosis; however, they do not differentiate between latent TB infection and active TB disease. Consequently, the Tuberculin skin test remains widely utilized for diagnosing tuberculosis worldwide. To combat this pervasive and deadly disease, it is essential to thoroughly understand the mechanisms of TB and to disseminate comprehensive information regarding its treatment.*

Keywords: Epidemiology, Mycobacterium tuberculosis, Tuberculin Skin Test, WHO

I. INTRODUCTION

Tuberculosis (TB) is a communicable disease that accounts for over one million cases annually in India. It is caused by the bacterium Mycobacterium tuberculosis. While it predominantly impacts the pulmonary system, it can also affect other organs if left untreated. In a 1990 report on the Global Burden of Disease, the World Health Organization (WHO) identified TB as the seventh leading cause of mortality worldwide. By 2001, the WHO estimated that approximately 32% of the global population was affected by TB. Each year, nearly 8 million individuals are diagnosed with the disease, and around 2 million succumb to it due to inadequate treatment. Tuberculosis is a potentially severe infectious condition that primarily targets the lungs. The bacteria responsible for TB are transmitted from one individual to another through minute droplets that are expelled into the air during coughing and sneezing.

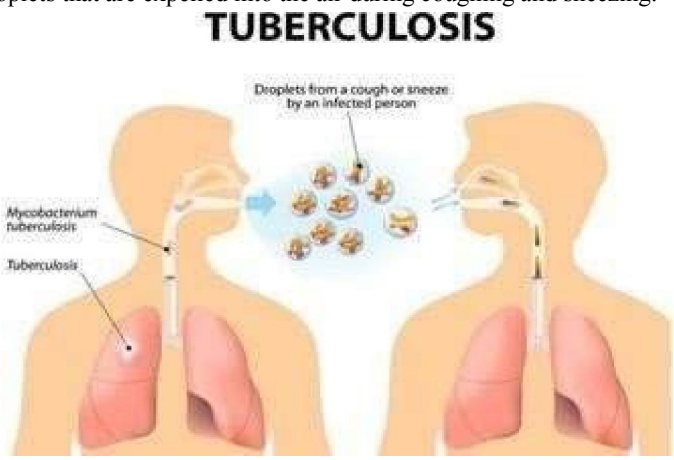

Figure 1: The spectrum of TB — from Mycobacterium tuberculosis infection to active (pulmonary) TB disease.

HISTORY OF TB

The advice to "just sleep and eat nutritious foods" was commonly given to patients suffering from tuberculosis (TB) in the 1800s, a disease caused by the airborne bacterium Mycobacterium tuberculosis. This pathogen primarily targets the

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lungs, resulting in symptoms such as severe coughing, fever, and chest pain. In 1882, German microbiologist Robert Koch identified Mycobacterium tuberculosis as the causative agent of TB in humans, marking a significant advancement in medical understanding. This discovery was further complemented by the development of tuberculin in 1890.

With the emergence of AIDS, TB incidence saw a resurgence, prompting renewed scientific interest in its research and prevention. Currently, the diagnostic and therapeutic resources available to combat TB have significantly improved, leading to strategic initiatives aimed at controlling the disease. Notably, the Directly Observed Treatment Short-Course (DOTS) strategy was introduced in 1993, followed by the DOTS-plus program in 1998 to tackle multidrug-resistant (MDR) TB. Despite ongoing research yielding valuable insights into TB transmission, detection, and treatment, substantial progress is still required to effectively reduce TB incidence.

The Bacillus Calmette-Guérin (BCG) vaccine was developed in the 20th century to prevent TB; however, despite widespread administration, it has not succeeded in curbing the disease's spread in densely populated regions. The persistent rise in infections in impoverished areas, even post-vaccination, can be attributed in part to the BCG vaccine's variable efficacy in preventing adult pulmonary TB. The transmission of Mycobacterium tuberculosis continues through active pulmonary cases, underscoring the urgent need for a more effective vaccine against TB.

According to the WHO Global Tuberculosis Report (2017), there were 490,000 cases of multidrug-resistant (MDR) TB, with only a 50% survival rate among patients who adhered to the recommended treatment regimens.

EPIDEMIOLOGY

It has been estimated that one-third of the global population is infected with Mycobacterium tuberculosis (MTB). This infection can transition from a latent state to an active form. Approximately 5 to 10% of individuals with latent tuberculosis infection (LTBI) are at significant risk of progressing to active tuberculosis (TB). Those who are HIV-positive or have other immunocompromising conditions, such as cancer or those undergoing immunosuppressive therapy, face an elevated risk of developing active TB. Robert Koch asserted that tuberculosis is more lethal than diseases such as plague or cholera, with around 9 million individuals worldwide infected with TB and approximately 1.5 million succumbing to the disease in 2013. In 2004, tuberculosis accounted for over 2.5% of global mortality, with infection rates particularly high in environments such as hospitals and prisons. The proliferation of TB in these settings is influenced by factors such as virulence, innate immunity, and susceptibility. While tuberculosis can manifest in any region, the majority of fatalities— approximately 95%—occur in low-income countries with limited resources, notably including India and China. Individuals who are HIV-positive are particularly vulnerable to TB infection, with 80% of HIV-positive patients residing in sub-Saharan Africa. In contrast, the United States, which has a smaller population, reports that only 10% of its TB patients are HIVpositive. In 2008, there were 12,904 reported cases of TB in the U.S., translating to a rate of 4.2 per 100,000 individuals. Despite advancements in diagnostics over the past four years, 80% of TB cases globally are concentrated in more than twenty-two countries, including India, Pakistan, Nigeria, Bangladesh, Indonesia, South Africa, and Russia.

TRANSMISSION

Tuberculosis (TB) infection is primarily spread through the inhalation of infectious particles expelled by an individual with TB during coughing or sneezing. A significant proportion of individuals who inhale Mycobacterium tuberculosis (MTB) bacteria may mount an effective immune response in the lungs, which can inhibit the proliferation of the bacteria, leading to a dormant state. This condition is referred to as latent tuberculosis infection (LTBI). Individuals with LTBI are infected with MTB but do not exhibit any clinical signs or symptoms, nor do they pose a risk of transmission to others. Certain populations are at a heightened risk of TB infection, including adult males, individuals residing in developing nations, healthcare workers exposed to TB, and those with compromised immune systems, such as individuals living with AIDS. Indeed, tuberculosis remains a leading cause of mortality among HIV infected patients, and the co-infection of HIV and TB is frequently observed. Furthermore, individuals born outside the country and those living in impoverished conditions or areas with prevalent malnutrition are also more susceptible to TB infection. Transmission of TB can also occur through aerosolized droplets from individuals with active TB. Patients who test positive for acid-fast bacilli (AFB) are at the highest risk of transmitting the infection. However, it is important

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to note that individuals with negative smear results but positive cultures can still spread the disease. Additional factors that may increase susceptibility to MTB infection include diabetes, prolonged use of corticosteroids, TNF-alpha inhibitors, and genetic variations in vitamin D receptors, as well as polymorphisms in the IL-12 and IFNgamma genes.

Factors	Description
Susceptibility	Susceptibility (immune status) of the exposed individual.
Infectiousness	Infectiousness of the person with TB disease directly related to the number of tubercle bacilli that he or she expels into the air.
Environment	Environment factors that affect the concentration of M. tuberculosis organisms.
Exposure	Proximity, frequency and duration of exposure.

Table 1: Factors determine the probability of transmission of M. tuberculosis).

TUBERCULOSIS INFECTION CONTROL

Administrative controls

- Perform a tuberculosis risk evaluation.
- Formulate and implement a documented plan for the control of tuberculosis (TB) infection.
- It is essential to conduct thorough cleaning and sterilization or disinfection of equipment that may be contaminated.
- Provide training and education for healthcare professionals.
- Assess and examine healthcare personnel for tuberculosis infection and disease.
- Implement principles of prevention grounded in epidemiological research.
- Environmental controls
- Decrease the concentration of infectious droplet nuclei by employing the following technologies:
- Ventilation technologies encompass a range of methods, including natural ventilation systems.
- Mechanical ventilation.
- High-efficiency particulate air filtration (HEPA).
- Ultraviolet germicidal irradiation (UVGI).
- Respiratory protection control
- Establish a program for respiratory protection.
- Educate healthcare professionals on the safeguarding of the respiratory system.
- Instruct patients on the principles of respiratory hygiene and emphasize the significance of covering their coughs.
- Wear mask for protection.

DIAGNOSIS OF TUBERCULOSIS

Consequently, the investigation of novel diagnostic and screening methodologies and criteria has become essential for the effective management of tuberculosis (TB). Latent tuberculosis infection (LTBI) is identified through the use of interferon gamma release assays (IGRAs); however, the tuberculin skin test (TST) remains a more cost-effective option for economically disadvantaged populations. Both TST and IGRA function by evaluating the immune T cell response to specific TB antigens.

Tuberculin skin test

In the Tuberculin Skin Test (TST), a protein derivative derived from the tuberculosis bacterium is administered intradermally to the patient. This procedure elicits a delayed hypersensitivity reaction, classified as Type 4, in individuals who are infected with mycobacteria. To assess the presence of tuberculosis infection, the diameter of the resultant skin reaction is evaluated, typically within a timeframe of 48 to 72 hours. The standard measurement ranges from 0.74 at 5 mm to 0.40 at 15 mm. Nonetheless, the TST may yield misleading results, producing falsepositive outcomes in individuals who have received the BCG vaccine and false-negative results in those who are immunosuppressed.

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At-risk populations	Positive TST reaction size (mm)
Patients with HIV infection Patients receiving immunosuppressive therapy Abnormal findings on chest radiography consistent with previous TB infection Persons who have come in close contact with and actively contagious patient	≥5
Patients with certain chronic conditions Patients with certain malignancies Foreign-born persons from high-incidence regions (>25/100,000) Employees and residents of high-risk facilities	≥10
Healthy people at low risk of TB	≥15

(Table 2: TST Results for Populations at Risk of TB)

Interferon-gamma release assays

The Interferon Gamma Release Assays (IGRAs) represent a more sensitive and specific diagnostic approach for tuberculosis (TB), exhibiting a sensitivity range of 81-88%, in contrast to the 70% sensitivity associated with the Tuberculin Skin Test (TST). However, IGRAs are associated with higher costs and require specialized techniques for implementation. This assay measures the release of the cytokine interferon-gamma (IFN-γ) from T cells that respond to specific antigens not present in the Bacillus Calmette-Guérin (BCG) vaccine. A blood sample is obtained from the patient, and the subsequent measurement of IFN-γ release is conducted. The guidelines governing the use of IGRAs are subject to frequent updates. In Canada and certain European nations, there have been recommendations for the concurrent use of IGRAs and TST to identify latent tuberculosis infection (LTBI), although neither test is definitive. Understanding the progression of TB from a latent to an active state poses significant challenges. To enhance diagnostic capabilities, it is essential to identify risk factors prevalent in both high and low burden countries, which will further our comprehension of the immune response to TB.

Test	Strengths	Limitations
TST test	High specificity in non-BCG-vaccinated populations Cost-effectiveness	Training required for administration and interpretation Return visit required in 48-72 h for test result Possible booster effect Possible false-positive and false-negative results
Interferon-gamma release assays	High specificity Only 1 patient visit required No confounding by BCG vaccination High cost	Blood withdrawal required Indeterminate results in those who are immunosuppressed and in those aged <5 year No capacity to differentiate between latent and active TB High cost
Chest X-ray	Ready availability Capacity to differentiate latent infection from active TB Not confirmatory	Low sensitivity and specificity Not confirmatory
Smear microscopy	Ease, speed, and cost-effectiveness of the technique A quantitative estimate of the number of bacilli Usefulness in determining infectiousness and in monitoring treatment progress	Low sensitivity No capacity to differentiate from nontuberculous mycobacteria

(Table 3: Test for TB: Strength and limitations).

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Chest Radiography

Chest radiography is recommended for all individuals undergoing assessment for latent tuberculosis infection (LTBI) or active tuberculosis (TB). Pulmonary TB, which arises from the endogenous reactivation of a latent infection, typically manifests as infiltrates located in the apical and posterior segments of the right upper lobe, the apical-posterior segment of the left upper lobe, and the superior segment of the lower lobe.

Smear Microscopy

Smear microscopy for the identification of acid-fast bacilli (AFB) represents the most expedient and cost-effective approach for diagnosing tuberculosis (TB).

Site	Diagnostic procedure
Tuberculous lymphadenitis	Excisional biopsy with culture
CNS TB	Characteristic CSF exam AFB smear and culture of CSF Polymerase chain reaction for TB of CSF
Pleural TB	Pleural biopsy with pathology and culture
Tuberculous pericarditis	Pericardiocentesis with culture
Skeletal TB	Needle biopsy and culture
Genitourinary TB	Biopsy and culture of masses Culture of urine

(Table 4: Diagnosis procedure of Common Extrapulmonary TB).

SIGNS AND SYMPTOMS

General clinical features of TB

A persistent cough lasting over three weeks, with or without the presence of sputum, may be accompanied by symptoms such as weight loss, fever or pyrexia, and nocturnal sweating. Additional concerning signs include hemoptysis (the presence of blood in sputum), chest pain, and general fatigue or weakness.

Symptoms of tuberculous meningitis

Gradual alterations in mental status that could advance to a comatose state over the course of several days to weeks may be accompanied by a mild fever.

Symptoms of skeletal TB may include the following

Back pain or stiffness, lower limb paralysis, with 50% of cases associated with Pott's disease, and tuberculous arthritis, which typically affects a single joint, most frequently the hip or knee, followed by the ankle, elbow, wrist, and shoulder.

Symptoms of gastrointestinal TB

Oral, anal, or gastrointestinal tract ulcers; dysphagia associated with esophageal disorders; abdominal discomfort resembling peptic ulcer disease due to gastric or duodenal infections; malabsorption linked to small intestine infections; and symptoms such as pain, diarrhea, or hematochezia resulting from colonic infections.

Signs of extrapulmonary TB

The clinical manifestations include confusion, coma, neurological deficits, chorioretinitis, lymphadenopathy, and cutaneous lesion

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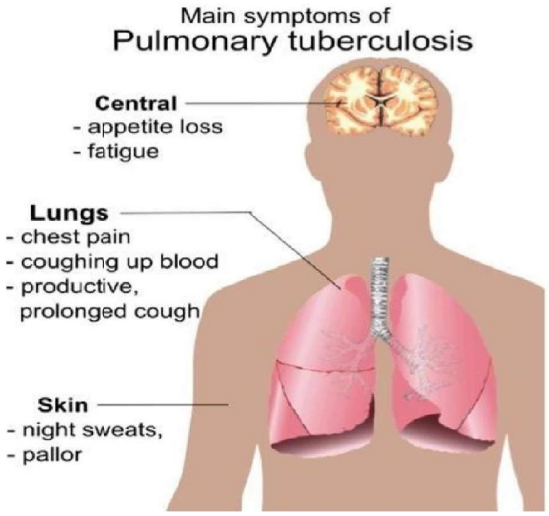

(Fig. 2: Image shows general symptoms of TB)

TREATMENT OF TUBERCULOSIS

Latent TB Infection

Treatment for latent tuberculosis infection (LTBI) is advised for individuals who are at a significantly elevated risk of progressing to active tuberculosis (TB). This treatment should commence only after a diagnosis of active TB has been confirmed through clinical evaluation and radiographic imaging. Neglecting to treat TB can lead to insufficient management and the emergence of drug-resistant strains, which poses a considerable challenge in contemporary healthcare. For the majority of patients, a 9-month regimen of Isoniazid (INH) is the preferred course of action. Additionally, it is advisable to provide Pyridoxine supplementation (25 mg/day) alongside INH for those at heightened risk of developing neuropathy. This includes individuals with existing peripheral neuropathy, nutritional deficiencies, diabetes mellitus, HIV infection, renal impairment, alcoholism, thyroid disorders, as well as pregnant or breastfeeding women. Intermittent treatment, specifically a twice-weekly schedule, should only be conducted under directly observed therapy (DOT). Given the significant incidence of hospitalization and mortality associated with liver damage, the combination therapy of Rifampin (RIF) and Pyrazinamide (PZA) is no longer recommended for LTBI management.

Active TB

Patients diagnosed with active tuberculosis (TB) require a regimen of multiple pharmacological agents to effectively eliminate the bacteria, minimize the potential for transmission, and avert the development of drug resistance. The optimal approach for managing TB involves directly observed therapy (DOT), which entails the supervision of patients as they ingest their antitubercular medications. Successful treatment hinges on a

patient-centered case management strategy and a collaborative effort between healthcare providers and local public health initiatives. Antitubercular medications are categorized into first-line and second-line agents. The first-line drugs include isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). Additionally, rifapentine and rifabutin, both rifamycin derivatives, are also classified as first-line treatments. Second-line medications encompass aminoglycosides such as streptomycin, kanamycin, and amikacin, along with various fluoroquinolones, including moxifloxacin, levofloxacin, and gatifloxacin. A collaborative statement regarding the treatment of TB in the United States has been released by the American Thoracic Society, the Centers for Disease Control and Prevention, and the **Infectious Diseases Society of America.**

Four treatment regimens are advised for individuals diagnosed with drug-susceptible tuberculosis (TB). While these regimens are generally applicable, it is essential to tailor treatment to the specific clinical circumstances of each patient. Each regimen consists of an initial phase lasting 2 months, followed by a continuation phase of either 4 or 7 months. The initial phase typically involves empirical treatment, as susceptibility data may not be readily available. To mitigate the risk of drug resistance and to optimize treatment efficacy, the initial phase should incorporate four medications:

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isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). If the bacterial isolate demonstrates susceptibility to INH and RIF, EMB may be omitted. Depending on the selected regimen, the initial phase medications can be administered daily throughout the treatment duration, daily for the first two weeks followed by biweekly doses, or three times weekly for the entire period. Treatment decisions during the continuation phase, which typically lasts 4 months for most patients, should be guided by susceptibility data. However, this phase may be extended to 7 months for specific patient groups: those with cavitary pulmonary TB whose sputum cultures remain positive after 2 months, patients whose initial treatment phase did not include PZA (such as those with severe liver conditions or pregnant individuals), and those receiving once-weekly INH and rifapentine whose sputum cultures are still positive after 2 months. Prolonging the continuation phase in these cases helps decrease the likelihood of relapse. During this phase, medications can be administered daily or 2 to 3 times weekly under directly observed therapy (DOT). The minimum treatment duration for culture-positive TB is 6 months, while if PZA is excluded from the initial phase, the treatment should extend to 9 months. Smear-negative, culturenegative pulmonary TB can be effectively treated with a 4-month regimen of INH.

Regimen	Drugs	Interval and Dose (duration)
1	INH, RIF, PZA, EMB	7 day/week for 56 doses (8 week)
2	INH, RIF, PZA, EMB	7 day/week for 14 doses (2 week), then twice weekly for 12 doses (6 week)
3	INH, RIF, PZA, EMB	3 times weekly for 24 doses (8 week)
4	INH, RIF, EMB	7 day/week for 56 doses (8 week)

(Table 5: Treatment Regimens of TB)

II. CONCLUSION

Tuberculosis continues to pose a significant global health threat. Efforts to eradicate this disease have been significantly hindered by factors such as poverty, inadequate access to healthcare, the emergence of drug-resistant strains, and the presence of immunocompromised individuals, including those infected with HIV or suffering from diabetes and other infections, as well as the dynamics of global migration. Effective management of tuberculosis necessitates a multifaceted approach that incorporates clinical evaluations, radiographic imaging, microbiological assessments, and histopathological examinations, alongside the initiation of appropriate multidrug regimens. Beyond the treatment of individuals with active tuberculosis, public health strategies must encompass accurate diagnosis, thorough contact tracing, and testing of individuals who have been in close proximity to active cases. The rising incidence of tuberculosis can be attributed to an increasing population, persistent poverty, and inadequate treatment practices. Short-course chemotherapy has emerged as a highly effective and beneficial method for treating tuberculosis. To address the issue of drug resistance and enhance the efficacy of treatment, it is essential to implement certain critical measures.

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