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A Review of Modern Therapeutic Approach to Treat Extra Pulmonary TB

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ABSTRACT

Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide. It is estimated that 25% of the world's population is infected with Mycobacterium tuberculosis, with a lifetime risk of 5 to 10% of progression to tuberculosis. Early recognition of tuberculosis and rapid detection of drug resistance are essential to contain its global burden. Culture, direct microscopy, biomolecular testing, and whole genome sequencing are established diagnostic methods; however, their widespread use is often limited by cost, local resources, time constraints, and operator efficiency. Methods to optimize these diagnostics, as well as the development of new techniques, are under investigation. The choice of an appropriate treatment regimen depends on the susceptibility profile of the isolate detected. Currently, 16 new drugs for the treatment of tuberculosis are being evaluated in phase I or II clinical trials and another 22 drugs are in the preclinical stage. Along with the development of these new drugs, most of which are oral medications, new shorter treatment regimens are being evaluated. The goal of these shorter treatment regimens is to encourage patient compliance and prevent relapse or the development of new drug resistance.

Extrapulmonary involvement may occur in isolation or in association with a pulmonary focus, as in patients with disseminated tuberculosis (TB). The recent human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) pandemic has led to a shift in epidemiology and has brought extrapulmonary tuberculosis (EPTB) back into focus. EPTB accounts for approximately 15–20% of all TB cases in immunocompetent patients and accounts for more than 50% of cases in HIV-positive individuals. Lymph nodes are the most common site, followed by pleural effusion, and almost any site in the body may be affected.

Keywords ; Tuberculosis, special population, pyrazinamide, ethambutol fluroquinolones

INTRODUCTION

In 1882, Robert Koch identified the bacterium responsible for tuberculosis (TB), a contagious airborne disease caused by the Mycobacterium tuberculosis complex. By 2016, TB remains a significant cause of illness and death, especially in low-income and middle-income nations. Although it mainly infects the lungs, M. tuberculosis can cause illness in various parts of the body. TB can manifest in many forms, ranging from asymptomatic infections to severe, lifethreatening conditions. Clinically and from a public health standpoint, TB patients are typically categorized as having either latent TB infection (LTBI), which is asymptomatic and not contagious, or active TB disease, which can be spread (notably in active pulmonary TB) and can be diagnosed using culture or molecular methods. Individuals suffering from active TB often experience general symptoms like fever, fatigue, reduced appetite, and weight loss, while those with lung involvement may have a persistent cough and cough up blood in advanced stages. Nevertheless, some patients with active, culture-positive TB may not show any symptoms and are viewed as having subclinical TB. The standard treatment regimen for TB consists of four primary medications: isoniazid, rifampicin, pyrazinamide, and ethambutol. Resistance to these drugs can develop, and multidrug-resistant TB (MDR-TB) — which occurs when M.tuberculosis is resistant to at least isoniazid and rifampicin — is widely acknowledged and reported in almost all countries. Extensively drug-resistant TB (XDR-TB) is an even more serious form of the disease, resistant not only to isoniazid and rifampicin but also to any fluoroquinolone and any of the three second-line injectable aminoglycosides. The diagnostic and treatment strategies differ for LTBI and active TB disease, as well as for drug-susceptible and drug-resistant TB. In this Primer, we will explore the epidemiology, microbiology, immunology, pathogenesis, diagnosis, treatment, and prevention of M. tuberculosis infection and TB, with a focus on drug-resistant TB, TB inn children, and Tb associated with HIV.

TRAMISSION

Tuberculosis spreads through aerosol droplets expelled by individuals suffering from active pulmonary disease. The risk of transmission is highest in patients with cavitary lesions or positive acid-fast bacilli (AFB) smears; however, those with negative smears yet positive cultures can also spread the infection. Various host factors significantly affect which individuals exposed to TB are at a higher risk of developing primary or active disease. Individuals with weakened immune systems, whether due to conditions like HIV or certain cancers, or due to immunosuppressive treatments such as corticosteroids, tumor necrosis factor α inhibitors, calcineurin inhibitors, and chemotherapy drugs, are particularly vulnerable.

CLINICAL MANIFESTATION

Primary Pulmonary TB:* Symptoms associated with the initial infection are termed primary pulmonary TB. These symptoms are typically mild and may include a low-grade fever. Approximately two-thirds of individuals with primary pulmonary TB remain symptom-free. Physical examinations usually yield normal results, while the most prevalent radiographic finding is hilar adenopathy. Other, less common findings may show pulmonary infiltrates in the mid to lower lung areas.

Reactivation TB: About 90% of TB cases in adults are due to reactivation TB. Symptoms emerge gradually and are most frequently characterized by fever, cough, weight loss, fatigue, and night sweats. Less frequently reported symptoms include chest pain, difficulty breathing, and coughing up blood. Physical exam results tend to be nonspecific, potentially revealing rales or signs of pleural effusion, such as dullness on percussion. Chest X-rays typically show infiltrates in the apical-posterior segment of the upper lobes, with up to 20% of these infiltrates indicating cavities filled with fluid. Although not unique to TB, CT scans may display a "tree in bud" appearance with centrilobular lesions, nodules, and branching linear patterns. Among the approximately 15% of patients without upper lung infiltrates, a variety of radiographic findings can occur, including lower lung infiltrates (particularly in the superior segments), nodules, effusions, and hilar adenopathy. Additionally, up to 5% of individuals with active pulmonary TB may show normal chest radiography findings, especially notable in HIV co-infected patients, who are more likely to have unusual (e.g., less involvement of the upper lobes) or normal radiographic results.

Endobronchial TB: Endobronchial TB arises from the direct spread of TB from lung tissue or from the introduction via sputum into the bronchial tree. Symptoms may involve a persistent cough with sputum production, and examinations might uncover rhonchi and wheezing; this wheezing can sometimes be mistaken for asthma.

Pleural TB:* Making up about 4% of all tuberculosis (TB) cases, pleural TB is the second most common form of extrapulmonary TB. Patients may experience general symptoms along with a dry cough and chest pain that is worsened by breathing. Chest X-rays usually indicate a unilateral effusion, while analyzing pleural fluid reveals a lymphocyte-dominant exudate with low glucose levels and acidity. Cultures from pleural fluid are positive in only around 30% of instances, but combining histological analysis with cultures from a closed pleural biopsy typically leads to a diagnosis in most cases.

Tuberculous Pericarditis: In developing countries, tuberculous pericarditis is likely the leading cause of pericardial effusion and constrictive pericarditis, though it is rare in wealthier nations. Patients may experience symptoms associated with pericardial effusion or constriction, including shortness of breath, cough, and swelling, alongside systemic symptoms like night sweats, mild fevers, and weight loss.

Skeletal TB: Occurring in 1% to 5% of TB patients, skeletal TB typically affects the thoracolumbar spine. Patients usually report localized pain at the site, though systemic symptoms may be absent. Diagnosis is confirmed by culturing specimens collected via needle aspiration or biopsy.

TREATMENT

Extrapulmonary tuberculosis: The same drugs are used to treat extrapulmonary tuberculosis as pulmonary tuberculosis. A treatment duration of 6 to 9 months is recommended. Cases with meningeal involvement should receive treatment for 9 to 12 months.12 Comparative data supporting this longer duration for meningeal disease are lacking. Clinical response should be closely monitored to extend treatment in patients who respond slowly. Patients with pericarditis or meningitis should also receive corticosteroids.

According to the ATS-CDC-IDSA guidelines for tuberculosis treatment, it is recommended to use ideal body weight for dosing antituberculosis medications. This guidance stems from a single case report and raises some concerns since weight and height can significantly influence the pharmacokinetics of first-line tuberculosis drugs. The initial treatment regimen for tuberculosis includes rifampin at 10 mg/kg (with a maximum of 600 mg), isoniazid at 5 mg/kg (maximum 300 mg), pyrazinamide at 15–30 mg/kg (maximum 2 g), and ethambutol at 15–20 mg/kg (maximum 1.6 g), all taken daily for 8 weeks. This is followed by a continuation

phase involving isoniazid at 15 mg/kg (maximum 900 mg) and rifampin at 10 mg/kg (maximum 600 mg), administered 2–3 times per week for an additional 18 weeks. A recent study suggests that employing a twice-weekly regimen or one that includes rifapentine during the continuation phase may be linked to a higher risk of relapse. As an alternative, the continuation phase could incorporate daily doses of isoniazid at 5 mg/kg and rifampicin 10mg/kg.

SPECIAL POPULATION

Existing liver disease: 6 months of treatment with rifampicin, ethambutol, and pyrazinamide may be used in patients with elevated aspartate aminotransferase (AST) levels. more than 3 times the upper limit of normal before starting anti-tuberculosis treatment.12 Hepatotoxicity can also occur in patients receiving rifampicin and pyrazinamide. A 9-month course of isoniazid and rifampicin can be used as an alternative treatment. These patients should also take ethambutol as a third drug until rifampicin and isoniazid susceptibility is established are available. Patients with severe liver disease should not take any or only one hepatotoxic drug. Treatment with rifampicin plus ethambutol for 12 months is suggested by instructions, with a fluoroquinolone used during the first 2 months of treatment. Alternatively, treatment with streptomycin, ethambutol, a fluoroquinolone, and another second-line agent does not contain hepatotoxic drugs. These recommendations are based on expert opinion.

Pregnant or breastfeeding women: All pregnant patients with a moderate to high probability of tuberculosis should be treated with rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, then rifampicin and isoniazid for another 4 months.

CONCLUSION

Extra pulmonary tuberculosis remains a major cause of morbidity and mortality. Thus, early diagnosis and initiation of appropriate treatment are important to reduce morbidity and mortality in patients with extra pulmonary tuberculosis. The availability of new molecular tests, liquid culture methods, computed tomography, magnetic resonance imaging, laparoscopy, and endoscopy has contributed significantly to the diagnosis of extra pulmonary tuberculosis. The disease usually responds to standard anti-tuberculosis treatment. A biopsy and/or surgery is required to collect tissue samples for diagnosis and management of complications. Further research is recommended to develop the most effective treatment for extra pulmonary tuberculosis.

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