Tuberculosis

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ABSTRACT

Tuberculosis (TB) resulted in 1.3 million deaths and 8.6 million new cases of active TB worldwide in 2012. Clinical manifestations of TB include fever, night sweats, weight loss, and cough. Latent infection is established by a positive tuberculin skin test or interferon-γ-release assay. Active TB disease is diagnosed by clinical, radiographic, and laboratory findings. Latent infection treatment is recommended in at-risk populations. The standard initial regimen for active disease includes rifampin, isoniazid, pyrazinamide, and ethambutol. Health-care providers are encouraged to consult with a TB specialist for assistance in the management of individuals with suspected or confirmed TB.

Keywords: acid-fast bacilli, ethambutol, interferon-γ-release assay, isoniazid, latent TB, multidrug-resistant TB, pyrazinamide, rifampin, tuberculin skin test, tuberculosis

Tuberculosis is one the most transmissible infectious diseases in the world. It is a significant cause of infectious disease–related death throughout the world (ranking second only to HIV) and ranks within the top 15 causes of death worldwide.[1,2] Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (MTb), an acid-fast bacillus bacteria. HIV has contributed to the resurgence of TB worldwide. In addition, the emergence of drug-resistant TB has increased the burden of TB disease.

EPIDEMIOLOGY

One third of the world's population is infected with TB.[3] In 2012, there were 8.6 million new cases of active TB and approximately 1.3 million TB-related deaths worldwide.[2-4] In the United States, in 2012, 9,945 TB cases (3.2 cases per 100,000 persons) were reported; this was the lowest number of cases since reporting began in 1953.[3] The number of TB cases in the US has decreased since the 1992 resurgence peak. In the US, the majority of TB cases occur among foreign-born individuals. In 2012, the case rate among foreign-born individuals was 11 times higher than among US-born individuals.[3,5-7] In addition, immunocompromised individuals are at greater risk for active TB (TB disease). HIV-infected individuals who also have latent TB infection are 21 to 34 times more likely to develop active TB.[3,4]

Throughout the world, the number the number of TB cases per year is also slowly declining (between 1992 and 2012, the death rate decreased by 45%).[2,4] The World Health Organization has a goal to reverse the spread of TB by 2015.[4] In 2012, Asia had the largest number of new TB cases (60% of new cases). However, sub-Saharan Africa had the highest proportion of new cases per capita (255 per 100,000). Other countries with high rates of TB include India, China, and the Russian Federation. Approximately 80% of TB cases in 2012 occurred in only 22 countries.[2,4,6]

PATHOPHYSIOLOGY

Once inhaled, the majority of droplet nuclei containing MTb are trapped in the upper airways and expelled by the cilia. The bacteria that escape expulsion reach the alveoli and, initially, multiply unopposed by host defense mechanisms. Cell-mediated immunity eventually kicks in to activate T lymphocytes and macrophages. The macrophages surround the MTb forming granulomas that limit replication and spread of the MTb. It is estimated that it takes 4 to 12 weeks for a delayed hypersensitivity reaction to occur and it is at this point that the skin test conversion can occur. Granulomas may later liquefy, resulting in reactivation. In individuals with impaired cell-mediated immunity, the disease may

initially present as primary pulmonary TB or, later on, as reactivation disease.[8-10]

TRANSMISSION

Latent TB infection (LTBI) occurs after the cell-mediated immune response, where progression is halted and the bacteria are contained in localized lesions. At this point, the individual is asymptomatic and noninfectious. Individuals with active pulmonary TB disease are contagious. TB is transmitted via droplet nuclei primarily from patients with positive acid-fast bacilli (AFB) smears.[7-10]

CLINICAL PRESENTATION

LTBI is not associated with clinical findings and is not contagious. However, individuals with LTBI may develop TB disease. In the US, more than 80% of active TB cases are the result of reactivation.[11] It is estimated that 10% of individuals with untreated LTBI will reactivate to active disease during their lifetime; this risk is highest during the first 2 years after infection. If an individual with LTBI becomes infected with HIV, that risk increases to 5% to 12% per year. If an HIV-infected individual acquires LTBI, the risk of active disease within 2 years is up to 50%, depending on the status of the immune system.[8,9,11]

Pulmonary disease can be classified as primary or reactivation. Primary pulmonary TB symptoms are generally mild and patients are relatively asymptomatic. Physical examination findings are unremarkable; lymphadenopathy may be present as well as hilar adenopathy on chest radiography. Classic symptoms of reactivation disease include fever, night sweats, weight loss, anorexia, fatigue, and cough (initially nonproductive but progresses to productive with purulent sputum), with or without hemoptysis. Physical examination findings are nonspecific but may include rales or dullness to percussion. Chest radiography may reveal infiltrates in the apical and posterior segments of the upper lobes. Cavitation may also be visible on chest radiography. However, not all patients will have traditional chest radiography findings and may have atypical (lower lobe infiltrates, hilar adenopathy) or normal radiographic findings.[7-10]

Before the HIV epidemic, the majority of TB cases were pulmonary, with the remaining 15% being extrapulmonary. However, in advanced HIV infection, extrapulmonary TB disease with or without pulmonary disease is more common. The risk increases as immune function decreases due to the immune system's inability to contain the MTb. Extrapulmonary disease may occur at any site, including bones, joints, lymph nodes, central nervous system, peritoneal space, pleura, and pericardium. Disseminated TB may also occur secondary to poor host defenses and is referred to as miliary TB. Miliary TB occurs more commonly in children and immunocompromised individuals. This form of TB may be rapidly fatal as patients can present with severe disease (ie, septic shock and acute respiratory distress syndrome[7-11]).

DIAGNOSIS

Screening and diagnosis are important strategies in identifying persons with MTb infection and disease. The screening tests cannot distinguish between infection (LTBI) and disease (active TB). Until recently, the tuberculin skin test (TST) was the only screening test to identify LTBI. The interferon-γ-release assays (IGRA) can also detect latent tuberculosis. Diagnosis of active TB is based on clinical, laboratory, and radiographic findings.

LATENT TB

Tuberculin Skin Test

The TST, also known as the Mantoux test, is an intradermal injection of 0.1 mL of 5 tuberculin units of purified protein derivative (PPD) into the dorsal or volar surface of the forearm. This screening test measures cell-mediated immunity via a delayed-type hypersensitivity to the PPD. Interpretation of the test is done 48 to 72 hours after administration. The injection site is examined by a trained health-care provider for induration, not erythema.[7,9-11]

Interpretation of the skin reaction is based on induration size, not erythema. Induration between 5 and 15 mm is considered positive for specific risk groups (Table 1). Individuals who have a positive TST are at increased risk of developing active TB disease. These individuals should receive drug therapy for LTBI. In an individual with a negative TST in the previous 2 years with a repeat positive TST, an increase of ≥10 mm is predictive of recent MTb infection.[7,9-12]