EDUCATIONAL COMMENTARY – TUBERCULOSIS PART I: AN OLD DISEASE WITH NEW THREATS

Educational commentary is provided through our affiliation with the American Society for Clinical Pathology (ASCP). To obtain FREE CME/CMLE credits, click on Earn CE Credits under Continuing Education on the left side of the screen.

Learning Objectives

On completion of this exercise, the participant should be able to

• discuss *Mycobacterium tuberculosis* and its significance;
• discuss the methods used for diagnosis of tuberculosis infection, including the advantages and disadvantages of each;
• compare active vs latent tuberculosis infections;
• summarize the antimycobacterial drugs used to treat tuberculosis as well as treatment recommendations; and
• explain multidrug resistant *M tuberculosis* and extensively drug-resistant *M tuberculosis*.

Introduction and History

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*, an acid-fast-bacillus. *M tuberculosis* bacteria are contagious and can be spread from person to person through coughing, sneezing, talking, or singing, via airborne droplets. Tuberculosis typically affects the lungs, but it can also affect other organs and systems in the body, such as the kidney, brain, and spine. Not everyone infected with *M tuberculosis* becomes ill. Some people become ill within weeks of being infected, before their immune system can fight the infection, but others get sick years later, when the immune system becomes weak for a reason other than TB. If a person is infected with *M tuberculosis* and the bacteria are living in the body but the person does not have symptoms, he or she has what is called a *latent TB infection* (LTBI). Generally, persons at risk for developing TB disease fall into two categories: (1) those who have recently been infected with *M tuberculosis* and (2) those with medical conditions that weaken the immune system.1

Tuberculosis is one of the most common deadly infectious diseases worldwide. Unfortunately, little progress has been made toward eliminating TB and the disease is an urgent public health problem, which is amplified by drug-resistant strains that are difficult and more expensive to treat. Currently, one-third of the world’s population, approximately 2 billion people, are infected with *M tuberculosis* but do not have active TB disease.2 Approximately 10% of people with LTBI develop active disease during their lifetime and become potentially infectious. Although TB is curable and preventable, in 2015, 10.4 million people became ill with TB and 1.8 million died of the disease.2 More than 95% of the TB deaths occurred in low- and middle-income countries. Distribution of TB correlates with poverty and human development indices.
EDUCATIONAL COMMENTARY – TUBERCULOSIS PART I: AN OLD DISEASE WITH NEW THREATS (cont.)

The six countries with the highest proportion of TB incidence are India, Indonesia, China, Nigeria, Pakistan, and South Africa. Combined, these countries account for 60% of all cases of TB. Poor social conditions such as malnutrition and inadequate housing with close living quarters facilitate the spread of M tuberculosis.3

Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals of the United Nations. To accomplish this goal, a 2020 milestone of the World Health Organization’s (WHO) End TB Strategy states infection rates must decline by 4% to 5% annually. This goal is idealistic: each year since 2000, the average decline has been only 1.5%.2

Stages of Tuberculosis Infection

The stages of TB disease are characterized by what occurs after the initial infection. Inhalation of aerosolized droplets containing M tuberculosis with deposition in the lungs leads to four possible outcomes:

- Immediate clearance of the organism
- Primary (active) disease: immediate onset of active TB disease
- Latent infection: presence of M tuberculosis without symptoms
- Reactivation disease: onset of active disease many years after a period of latent infection.4

After initial exposure and infection of alveolar macrophages, the progression of disease depends on the person’s cellular immunity, amount of exposure to the M tuberculosis organisms, and virulence of the strain. In most individuals, a cellular immune response is initiated following initial exposure. T cells arrive within 4 to 6 weeks, with cytokines (including interferon gamma) that enable the white blood cells at the site of infection to destroy the intracellular mycobacteria. After initial infection, with adequate cellular response, a granuloma is formed consisting of immune cells at the site of infection.4 After the initial infection heals, the organisms are not totally eradicated, but are walled off in the granuloma, resulting in LTBI. During LTBI, the patient does not feel sick or have any symptoms, is not infectious to others, and the mycobacteria cannot be isolated in sputum or tissue cultures. Changes in the patient’s health that weaken the immune system can cause the M tuberculosis bacteria to become active and multiply, leading to an active infection later in life.1,4

Approximately 5% of immunocompetent persons progress to primary TB disease after initial exposure because their immune response is inadequate during primary exposure, the strain is highly virulent, or exposure to the M tuberculosis bacteria is high.4 However, active pulmonary disease most often develops in persons with compromised immune systems, such as those with human immunodeficiency
EDUCATIONAL COMMENTARY – TUBERCULOSIS PART I: AN OLD DISEASE WITH NEW THREATS (cont.)

virus (HIV), malnutrition, diabetes, or people who use tobacco, owing to an inadequate cellular immune response. The most common disease progression seen after exposure to tubercular organisms is to pulmonary disease. However, once exposed, the \( M \) \( tuberculosis \) organisms are picked up by dendritic cells, which can transport bacilli to lymph nodes, and the disease can disseminate through the bloodstream. The most common sites of spreading include the spleen, liver, bone marrow, and kidneys. Disseminated extrapulmonary disease can occur during primary infection or during reactivation of the disease.

Primary TB disease, or active TB infection, exhibits nonspecific symptoms such as fever, shortness of breath, night sweats, chills, fatigue, anorexia, and weight loss. These symptoms can be mild and progress over many months, which may result in a delay of diagnosis and increase the possibility of transmission to others. Persons with active TB can infect as many as 10 to 15 other people through close contact over the course of a year.

Risk factors for developing TB disease after exposure to \( M \) \( tuberculosis \) organisms include a weakened immune system. This includes infants, children, and elderly persons. Medical risk factors that leave a person susceptible to developing TB disease include the following conditions: HIV infection, substance abuse, diabetes mellitus, severe kidney disease, organ transplants, head and neck cancer, low body weight, silicosis, and medical treatments such as corticosteroids or immunosuppressant drugs for rheumatoid arthritis and Crohn’s disease. Coinfection with HIV is a significant risk factor for developing TB disease and increases the risk of mortality. People living with HIV are 20 to 30 times more likely to develop TB and 35% of all HIV deaths in 2015 were a result of active TB infection. Infection with HIV increases the likelihood that LTBI will progress to active disease, shortens survival times, and increases the likelihood of dissemination of the \( M \) \( tuberculosis \) bacteria throughout the body. Tobacco use also greatly increases the risk for TB disease and death. Smoking contributes to more than 20% of TB cases worldwide.

A vaccine is available for prevention of \( M \) \( tuberculosis \) infections, the bacille Calmette-Guérin (BCG). This vaccine is used in countries with a high prevalence of TB to prevent childhood tuberculous meningitis and miliary TB disease. Miliary tuberculosis is the clinical disease that results from hematogenous dissemination of \( M \) \( tuberculosis \), which is characterized by tiny tubercles seen on pathological examination which resemble millet seeds in size and appearance. The vaccine is not administered in the United States unless specific criteria are met and an expert on TB has been consulted. The reasons for this are that there is a low risk for exposure to \( M \) \( tuberculosis \) in the United States, and the BCG vaccine has shown limited effectiveness at preventing pulmonary TB disease in adults.
Diagnosis of Latent Tuberculosis Infection

Various methods are used to detect TB infection. The first two tests, often called “screening tests,” are the TB skin test (TST) and the TB blood test (interferon-gamma release assay [IGRA]). A person’s health care provider should choose which TB test to use. Factors to consider include the reason for testing, test availability, and cost. Using both a TST and an IGRA is not recommended. Neither test can distinguish active disease from latent infection, so they are better used to assess candidates for LTBI treatment. The diagnosis of LTBI is made when a patient has a positive result on TB test and his or her medical evaluation does not indicate active TB disease.

The TST or purified protein derivative (PPD) skin test is also referred to as the Mantoux tuberculin skin test. This in vivo TB skin test requires two visits with a health care provider. On the first visit, the test is performed by injecting a small amount of fluid (tuberculin) into the skin of the forearm. The patient must return within 48 to 72 hours to have a trained clinician look for a reaction at the spot of inoculation. The TST is based on the fact that infection with \textit{M. tuberculosi}s produces a delayed-type hypersensitivity skin reaction to certain components of the bacterium. A skin reaction is observed when T cells, which have been sensitized by a previous infection, are recruited to the skin site and release lymphokines. The lymphokines are responsible for the induration that occurs in infected patients. The induration is a hard, raised area with clearly defined margins at or around the injection site. It is produced through local vasodilation edema, fibrin deposits, and other inflammatory cells at the site. A positive test result is determined by measuring the size of induration after 48 to 72 hours. The size of induration for a positive result is based on the risk level of the patient. A positive TST means the person has been infected with \textit{M. tuberculosi}s at some point, but additional tests are needed to determine whether he or she has latent TB infection or active TB disease. The TST requires proper administration by the Mantoux method, and the patient must return for the reading. The test results can be affected by the person reading the test, or not be completed if the patient does not return for the reading. False-negative results can occur in immunosuppressed patients, and false-positive results can occur in persons with BCG vaccination or those who have been infected with nontuberculous mycobacteria.

An interferon-gamma release assay (IGRA) is an in vitro blood test that measures immune response to \textit{M. tuberculosi}s. It is an alternative to the TST, results in higher overall costs, and evaluation must be performed in the clinical laboratory. There are currently two IGRA approved by the US Food and Drug Administration: the QuantiFERON-TB Gold In-Tube test (Qiagen; QFT-GIT) and the T-SPOT.\textit{TB} test (Oxford Immunotec; T-SPOT). These tests detect and quantitate the cytokine interferon gamma, which is produced by T lymphocytes stimulated with tuberculin PPDs or \textit{M. tuberculosi}s. Owing to its ability to quantitate the differential response to the tuberculin PPDs, an IGRA can discriminate between true
EDUCATIONAL COMMENTARY – TUBERCULOSIS PART I: AN OLD DISEASE WITH NEW THREATS (cont.)

*M tuberculosis* infection and previous vaccination with BCG. A positive IGRA means the person has been infected with *M tuberculosis* at some point, but additional tests are needed to determine whether the person has latent infection or active disease.\(^1\) False-positive results can occur with the QFT-GIT in individuals with other mycobacterial infections, as the genes encoding for simulated proteins used in the assay are also present in *Mycobacterium kansasii*, *Mycobacterium szulgai*, and *Mycobacterium marinum*.

False-negative and false-positive results can be obtained with both the TST and IGRA testing methods; for this reason, all test results should be correlated with clinical history, radiographic findings, and other medical diagnostic tests. The TST and IGRA methods have similar sensitivity, but the IGRA methods are presumed to be more specific, as they should produce fewer false-positive results. False-positive results can occur for the TST in those individuals who have received the BCG vaccine or those with nontuberculous infections. The TST cannot differentiate BCG-vaccinated individuals from those with latent TB.\(^5\) The proteins used in the IGRA are not found in the BCG vaccine so previous vaccination with BCG will not result in a false positive, which is a significant advantage over the TST. Interferon-gamma release assays are preferred or recommended by the Centers for Disease Control and Prevention (CDC) for testing individuals from groups with historically low rates of returning to have skin tests read and for individuals who have received BCG vaccination. The TST is preferred for testing children aged younger than 5 years and can also be used in conjunction with IGRAs to increase diagnostic sensitivity in this age group.\(^5\)

**Diagnosis of TB Disease**

Tuberculosis is diagnosed by the patient’s medical history, physical examination, chest x-ray, and other laboratory tests, including detection of *M tuberculosis* through smear microscopy, cultures, or molecular diagnostics.\(^1\) The diagnosis of TB requires key epidemiologic risk factors combined with suggestive clinical and radiographic findings, followed by the definitive diagnosis, which requires culture confirmation of *M tuberculosis*.

Tuberculosis should be suspected in a patient with an unexplained weight loss, night sweats, fever, and fatigue. Pulmonary TB disease also includes a cough lasting more than three weeks, coughing up blood, and chest pain. If TB disease is suspected, a clinician should examine the patient’s history of TB exposure, consider demographic factors that may increase the risk of exposure to TB, and determine whether the patient has any risk factors, such as HIV infection or tobacco use, that increase the risk of latent TB infection progressing to active TB disease.\(^1\)
A chest x-ray will be performed if a patient has a positive TST or IGRA result and/or exhibits clinical signs and symptoms of disease. The x-rays are examined for chest abnormalities, including lesions appearing on the lungs, which may differ in size, shape, density, and cavitation. Chest radiography alone cannot reliably diagnose TB or distinguish between active and latent TB. It may be useful to rule out the possibility of pulmonary TB in a person with a positive reaction to a TST or IGRA but no symptoms of disease. If atypical findings are seen on the chest radiograph and the patient exhibits clinical symptoms and epidemiologic risk factors, further laboratory investigation is required to confirm the diagnosis of TB disease.

For the diagnostic confirmation of TB disease, a specimen must be collected from the patient and sent to a clinical microbiology laboratory for detection and isolation of *M. tuberculosis*. Traditionally, this is accomplished by performing a direct concentrated smear microscopic examination for acid-fast bacilli in conjunction with a mycobacterial culture. Newer molecular methods use nucleic acid amplification to detect *M. tuberculosis* bacteria from both clinical specimens and culture growth. One of these methods can simultaneously detect rifampin drug resistance. The detection of *M. tuberculosis* from unprocessed clinical specimens can decrease turnaround time by weeks and allow for faster diagnosis and treatment of TB. These methods will be discussed in a future 2018 Microbiology Educational Commentary, “Tuberculosis Part II: Diagnostic Testing for Detection and Treatment.”

**Tuberculosis Treatment**

Latent TB infections and active TB disease need treatment. Latent TB infections must be treated to prevent the development of active TB disease, and persons with a current active infection need treatment to resolve the infection and to prevent spread to others. Without proper treatment, 45% of HIV-negative people with TB disease and nearly all HIV-positive people with TB will die.

Directly observed therapy (DOT) is the most effective strategy for ensuring that patients with TB adhere to treatment and is a global strategy to prevent drug resistance of *M. tuberculosis*. In DOT, a trained health care worker or other designated individual (excluding a family member) provides the prescribed TB medications and watches the patient swallow every dose. It is not required for all patients with TB infections but it is recommended, as it ensures adherence to the treatment regimen, improves patient outcomes, and decreases *M. tuberculosis* drug resistance. Electronic DOT (eDOT) is an alternative method to in-person DOT, in which a patient is remotely observed (e.g., over a computer or smartphone) taking his or her TB medication. Electronic DOT was developed because DOT is resource-intensive, time-consuming, and often inflexible or centered around the providers, not the patient (the patient must go to the health care facility to take medication).
Treatment of patients with active TB disease is complicated and should be guided by antimicrobial susceptibility results, when available, and an infectious disease physician. In general, antituberculosis regimens consist of two phases: (1) an intensive phase lasting 2 months and (2) a continuation phase lasting 4 to 7 months. First-line anti-TB drugs that are the core of the treatment regimens include isoniazid, rifampin, pyrazinamide, and ethambutol. During the intensive phase, all four anti-TB drugs are taken simultaneously to achieve maximum effect. The drugs are taken at precise dosing regimens and intervals, with daily therapy preferred. This regimen is intended to prevent resistance to the anti-TB drugs, decrease the \textit{M tuberculosis} burden, and improve patient outcomes. At the end of the intensive phase, a clinical assessment, chest radiograph, and sputum collection for acid-fast bacillus smear and culture should be repeated. Once the intensive phase is completed, the continuation phase begins and should last for 4 to 7 months, making the total therapy time 6 to 9 months. The continuation phase uses two anti-TB drugs, usually isoniazid and rifampin, if the \textit{M tuberculosis} patient isolate is susceptible.

The treatment should be modified based on susceptibility data once it is available, regardless of the phase of treatment. Late-generation fluoroquinolones such as levofloxacin or moxifloxacin also have activity against \textit{M tuberculosis} and may be used to treat patients with resistance or intolerance to one of the first-line drugs.

Treatment of LTBI consists of isoniazid, isoniazid and rifapentine, or rifampin. The preferred method recommended by the CDC for those with LTBI is a daily dose of isoniazid for 9 months, or of rifampin daily for 4 months if an alternative is necessary. If the patient has been exposed to drug-resistant TB, a consultation with a TB expert is advised.

High-level adherence to the treatment regimen is required to prevent relapse and drug-resistant \textit{M tuberculosis}. Drug-resistant TB is more common in persons who do not take their medications regularly or do not finish all phases and doses of the drugs, are prescribed incorrect therapies, come from an area of the world where drug-resistant TB is common or have spent time with someone who is known to have drug-resistant TB, and in patients who develop TB disease again after being treated in the past.

There are several classifications of drug-resistant TB. \textit{Drug-resistant TB} refers to strains of \textit{M tuberculosis} that are resistant to at least one anti-TB drug. \textit{Multidrug resistant TB} (MDR TB) is defined as \textit{M tuberculosis} that is resistant to at least isoniazid and rifampin. \textit{Extensively drug-resistant TB} (XDR TB) is an uncommon type of MDR TB that is resistant to isoniazid and rifampin plus any fluoroquinolone and at least one of the injectable second-line drugs including kanamycin, amikacin, and capreomycin. The drug-resistant \textit{M tuberculosis} strains do not respond to standard treatment regimens of first-line anti-TB drugs. Treatment of patients with MDR TB and XDR TB becomes more complicated and expensive,
requiring up to two years of therapy with much more powerful, toxic drugs.\textsuperscript{8} Drug-resistant TB threatens the ability to stop the spread of this deadly disease. Globally, it is estimated that 4\% of new TB and 20\% of recurrent infections are MDR TB.\textsuperscript{8} In addition, MDR TB accounts for approximately 10\% of all TB deaths.\textsuperscript{3}

**Conclusion**

Tuberculosis is a devastating disease, especially in those coinfected with HIV. It is more prevalent in low- and middle-income countries with poverty and poor social conditions. Patients with *M tuberculosis* infection should be diagnosed as having active TB disease or LTBI. Persons with active TB disease exhibit clinical symptoms, have abnormal findings on chest radiograph, are infectious to others, and microbiology laboratory testing including culture should be performed to confirm their diagnosis. Those with LTBI do not exhibit symptoms and are not infectious. Diagnostic tests approved as indirect tests for *M tuberculosis* infection include the TST and IGRAs. These tests should be used in conjunction with clinical symptoms, patient history, risk assessment, radiography, and other medical diagnostic evaluations to diagnose TB. Tuberculosis is a major cause of death globally, and progress in the control of the disease is threatened by drug-resistant strains. Treatment is necessary for both active TB disease and LTBI to prevent the spread of *M tuberculosis*, to relieve the symptoms and decrease mortality in those with active disease, and to prevent the emergence of drug-resistant *M tuberculosis*.

**References**


EDUCATIONAL COMMENTARY – TUBERCULOSIS PART I: AN OLD DISEASE WITH NEW THREATS (cont.)


© ASCP 2017