Learning Outcome: Upon completion of this continuing education course, you will demonstrate a current, evidence-based understanding of the scope of tuberculosis (TB) infections, testing and treatment options, and infection control and prevention measures for the public and other healthcare providers.

Learning Objectives

- Trace the history of early TB treatments.
- Explain the prevalence, transmission, and pathogenesis of TB.
- Identify high-priority groups for testing and explain the appropriate testing methodologies.
- Distinguish between latent TB infection (LTBI) and TB disease and their treatments.
- Describe multidrug-resistant TB (MDR-TB) causes and treatment.
- Identify the best medication regimen for each special circumstance of TB.
- Outline the appropriate steps for TB infection prevention in healthcare settings.
- Discuss the primary considerations and measures for community TB prevention.

History of Tuberculosis

Tuberculosis (TB) is one of the most deadly diseases in the world today, killing nearly 1.5 million people annually, mostly in developing countries and lower- and middle-income settings. About one third of the world population has latent TB (WHO, 2016a). At least 9 million people become newly infected with TB every year, and an estimated 3 million new cases each year go undetected, causing further transmission. In the United States, it was at one time the leading cause of death, but TB mortality has decreased in recent decades (Keshavjee et al., 2015).
TB is caused by *Mycobacterium tuberculosis*, which usually attacks the lungs. This bacteria is most commonly spread when someone with active TB disease expels the bacteria in airborne droplets by coughing, sneezing, speaking, singing, etc.

Evidence of tuberculosis has been discovered in the skeletal remains of prehistoric bison and humans as well as in Egyptian mummies. In ancient Greece, Hippocrates wrote in his *Aphorisms* that *phthisis* (“consumption,” now known as TB) was the most widespread disease. Throughout the following centuries, consumption was identified by fatigue, night sweats, weight loss, and a general “wasting away” of the victim. Other common symptoms included coughing-up of thick white phlegm and blood. No effective treatments were available, and the disease continued as a leading cause of death.

**Understanding the Disease**

Over time, scientists gradually increased their understanding of the disease:

- In his 17th-century book *Opera Medica*, the Italian Sylvius identified tubercles, or round nodules, as a consistent and characteristic change in the lungs and other anatomical areas of consumptive patients.
- In an article published in 1839, the German J. L. Schönlein coined the term *tuberculosis* to describe what had by then been identified as a single disease.
- In a paper given in 1865, the French pathologist Jean-Antoine Villemin declared tuberculosis to be contagious.
- On March 24, 1882, in an historic lecture, German microbiologist Robert Koch reported having used a staining procedure to isolate the rod-shaped bacillus now known as *Mycobacterium tuberculosis*, for which he was later awarded a Nobel Prize (Schoenstadt, 2008). The date of his lecture is still observed as World TB Day.

**Early Efforts Toward Prevention and Cure**

Villemin and Koch’s discoveries did not lead to a cure. They did, however, impact the popular view of the disease and its victims. With the knowledge that the disease could easily be spread by a cough or sneeze, public health campaigns were mounted to protect against its transmission. In many cases, those who were already infected were feared by the healthy, often losing their jobs or housing (UVA, 2013).

During this era, attempts to treat or even cure TB patients led to the development of the *sanatorium* and “open-air” treatment. In the 1850s in Germany, Hermann Brehmer built the first sanatorium, a place where patients could get plenty of fresh air and good nutrition, after having spent time himself in the Himalayas as a successful treatment for his own TB. Thereafter, such sanatoriums began to flourish throughout Europe.
In the United States, Dr. Edward Livingston Trudeau read about the European “rest cure” in cold, clear mountain air. He himself had recuperated from TB in the Adirondack Mountains of New York by following a healthy diet and an outdoor exercise regime. His experiments while there on tubercular rabbits further supported his hypothesis that rest, exercise, and fresh air could cure the disease, and in 1885 he opened Adirondack Cottage Sanatorium, the first of its kind in this country. By 1904, there were around 100 such sanatoriums and Trudeau was elected president of the new National Association for the Study and Prevention of Tuberculosis, which later became the American Lung Association (UVA, 2013).

Following shortly after Koch’s report in 1882, Italian doctor Carlo Forlanini developed an apparatus for inducing artificial pneumothorax (lung collapse) as a treatment for tuberculosis. Having performed the technique for thirty years, along with a growing number of other physicians, he presented an authoritative report on his work in 1912 at the Seventh International Tuberculosis Conference in Rome. The technique was thereafter widely adopted in the United States and Europe (Sakula, 1983).

**Vaccination and Drug Treatment**

The development of sanatoriums helped in providing a haven for those healing from tuberculosis. Scientists and doctors continued their research in the hopes of finding a reliable cure for the disease.

In 1921 in France, the first TB vaccine was administered to humans. The Bacillus Calmette-Guérin (BCG) vaccine had been derived by Albert Calmette and Camille Guérin at the Pasteur Institute from a strain of *Mycobacterium bovis*. Since that time, many different strains of the BCG vaccine have been derived and are used today throughout the world, particularly in countries with a high incidence of TB.

It took over 20 more years for scientists to discover an effective drug remedy for tuberculosis. In 1943 at Rutgers University, the laboratory of Selman A. Waksman first purified *Streptomyces griseus*, which was soon developed into the first antibiotic treatment for the disease, called streptomycin. (This drug is no longer a first-line treatment for tuberculosis.) It was Waksman who coined the term *antibiotic*, and he too was awarded a Nobel Prize for his work.

Drug-resistant strains of TB emerged almost immediately after the introduction of streptomycin, and a rapid succession of other anti-TB drugs appeared in the following years. Antibiotics continue as the treatment for tuberculosis, most commonly used in combination to reduce the risk of developing resistance.

People who are infected but do not have TB disease are asymptomatic and not infectious; they usually have a positive reaction to the tuberculin skin test. Many people who have latent TB infection (LTBI) never develop active TB disease, although this group serves as the largest reservoir for those who may develop the disease. As many as 2 billion people worldwide may have LTBI. In people who have weak immune systems, the bacteria become active and cause TB
disease. Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site or as a disseminated disease (Turetz & Ma, 2016).

PREVALENCE

TB Worldwide

While TB cases have been drastically reduced in the United States and now pose a threat primarily to the elderly and immunocompromised, TB remains a killer of millions in developing countries. According to World Health Organization (WHO) estimates, one third of the world’s population is infected with M. tuberculosis. It is the second-leading cause of death from an infectious disease worldwide (after human immunodeficiency virus [HIV]).

In 2011, 8.7 million became infected with TB and 1.4 million died worldwide. Over 95% of the deaths occur in developing countries. It is among the top three causes of death for women aged 15 to 44. However, the number of people developing TB disease diminishes slowly each year, and the TB death rate diminished 25% from 1990 to 2015 (Keshavjee et al., 2015).

In an international conference in Geneva in May 2016, the WHO launched a campaign called “End TB Strategy” with a list of guidelines called “The Essentials,” planning to end global TB by 2030 (WHO, 2016a). The Millennium Development Goal target of stopping and reversing the TB epidemic by 2015 has been met globally. TB rates have fallen by 1.5% per year since 2000 and are now 18% lower than in 2000 (WHO, 2016b).

Sub-Saharan Africa has the highest rates of active tuberculosis per capita, primarily because of the HIV epidemic. The absolute number of cases is highest in Asia, with India and China having the greatest burden of disease globally, driven by population figures (Zumla et al., 2013).

Trends in the United States

Despite their drastic decrease throughout the twentieth century, in the late 1980s, TB cases started increasing again and peaked in 1992. This was attributed to several factors:

• The onset of the HIV epidemic and its related immunosuppression
• Increases in immigration of persons from countries where TB disease was common
• TB transmission in congregate settings (e.g., correctional facilities, long-term care facilities, homeless shelters)
• The development of multidrug-resistant TB (MDR-TB) (CDC, 2015)
Because of this rise in TB, federal and state funding for TB control was increased to help health departments and other organizations boost their efforts to prevent and control the disease. These efforts seem to have been successful, and since 1992, the overall number of TB cases in the United States has been steadily declining (CDC, 2015).

The national TB case rate is 2.96 per 100,000 population. The TB rate has declined 1.5% to 2.2% every year since 1982. The states with the larger percentages of foreign-born individuals showed a proportionately larger incidence of TB cases.

In 2014, 66% of all reported TB cases in the United States occurred in foreign-born persons. The case rate among foreign-born persons (15.4 per 100,000) was approximately 13 times higher than the rate among U.S.-born persons (1.2 per 100,000). The TB case rate of foreign-born individuals just entering the United States is comparable to that of foreign-born people currently living in the country (CDC, 2015).

The incidence among certain ethnic groups is disproportionate among the U.S. population:

- Asians: 17.8 cases per 100,000
- Pacific Islanders: 16.9 cases per 100,000
- African Americans: 5.1 cases per 100,000
- Native Americans: 5 cases per 100,000
- Hispanics or Latinos: 5 cases per 100,000
- Whites: 0.6 cases per 100,000

(CDC, 2015)
TRANSMISSION

*Mycobacterium tuberculosis* is spread from person to person through the air. When a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings, droplet nuclei containing tubercle bacilli (*M. tuberculosis* organisms) are expelled into the air. Depending on the environment, larger droplets will fall almost immediately to the ground, while tiny particles can remain suspended in the air for longer periods of time (Yates et al., 2016).

When a susceptible individual inhales droplet nuclei containing the tubercle bacilli, TB transmission may occur. The primary factors that affect the probability that TB will be transmitted include:

- Number of tubercle bacilli an individual expels into the air
- Severity of infectiousness of the individual with TB disease
- Environment in which exposure occurred
- Duration of exposure
- Virulence of the organisms
- Immune system of the recipient

(Yates et al., 2016)

**Drug-resistant TB** is transmitted in the same way as drug-susceptible TB, although it is no more infectious than drug-susceptible TB. However, delay in the recognition of drug resistance and resultant prolonged periods of infectiousness may facilitate increased transmission (CDC, 2013e).

Except for laryngeal TB, **extrapulmonary TB** (EPTB) (which occurs in places other than the lungs, such as lymph nodes, pleura, brain, kidneys, joints, and bones) is rarely contagious. Symptoms of extrapulmonary TB can mimic many other illnesses depending on the organ system that is affected (Zumla et al., 2013).

In the hospital, the best way to stop the transmission of suspected or confirmed infectious TB disease is to place the patient in a private room with Airborne Precautions instituted and then immediately begin effective TB therapy. Infectiousness declines rapidly after adequate standardized therapy is started, as long as the patient adheres to the prescribed regimen (Yates et al., 2016).

**RISK FACTORS**

There are a number of factors that put people at a higher risk for exposure to *M. tuberculosis*. Those at high risk include:

- Close contacts of those known or suspected to have active TB disease (e.g., family members, roommates, friends, coworkers)
• Foreign-born persons from areas of the world with a high incidence of active TB disease (e.g., Africa, Asia, Eastern Europe, Latin America, Russia)
• Visitors to areas with a high prevalence of TB disease, especially if visits are frequent or prolonged
• Residents or employees in high-risk congregate settings
• Healthcare workers who serve clients at increased risk for active TB disease
• Populations defined locally as having an increased incidence of latent tuberculosis infection or active TB disease (e.g., medically underserved, low-income populations, substance abusers)
• Infants, children, and adolescents exposed to adults at increased risk for latent tuberculosis infection or active TB disease
• Persons with a weakened immune system:
  o Babies, young children, the elderly
  o Substance abusers
  o Silicosis patients
  o Diabetes mellitus patients
  o Severe kidney disease patients
  o Those with low body weight
  o Head and neck cancer patients
  o Those undergoing medical treatments such as corticosteroids, organ transplant, specialized treatment for rheumatoid arthritis, or Crohn’s disease

Source: CDC, 2016a.

CASE

Leilani reports to the health clinic at school complaining of a nagging, productive cough. She tells the nurse practitioner, Duane, at the clinic that her college roommate has had the same symptoms for two months, but she didn’t think anything of it because she figured it was due to her roommate’s habit of smoking a pack of cigarettes a day.

When questioned, Leilani also tell Duane that her roommate spent the entire summer break on a medical mission in a clinic in Ghana. Duane explains that he will be doing a skin test on Leilani to check for tuberculosis and that her roommate will also need to come in for testing. If the tests are positive, the public health department will be notified and treatment will be started immediately.
PATHOGENESIS

Infection occurs when a susceptible individual inhales droplet nuclei containing tubercle bacilli and the droplet nuclei reach the alveoli (small air sacs) of the lungs. The tubercle bacilli that reach the alveoli are ingested by alveolar macrophages, and the majority of these bacilli are destroyed or inhibited.

A small number of the bacilli multiply intracellularly and are released when the macrophages die. If they are alive, these bacilli may spread through the bloodstream to more distant tissues and organs, including areas in which TB is most likely to develop: the apex of the lung, kidneys, brain, bones, and through the lymphatic channels to regional lymph nodes.

This process of dissemination primes the immune system for a systemic response. Immune responses soon develop to thwart the bacilli. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression (Niemi, 2014).

Latent TB Infection (LTBI)

An individual can thus have TB infection without progressing to TB disease. The initial stage is called latent TB infection, and it may be detected by using the Mantoux tuberculin skin test or the QuantiFERON-TB Gold (QFT-G) test (see “TB Testing” below). Individuals who are infected with *M. tuberculosis* but do not have TB disease cannot spread the infection to other people. Therefore, an individual with LTBI is not regarded as a “case” of TB for public health reporting (Collins et al., 2016).

TB Disease

In some people, the tubercle bacilli overcome the defenses of the immune system and begin to multiply, resulting in the progression from LTBI to TB disease. This process may occur soon after or many years after infection. In the United States, unless treated, approximately 5% of individuals who have been infected with *M. tuberculosis* will develop TB disease in the first year or two after infection, and another 5% will develop TB disease at some time later in life. Thus, approximately 10% of individuals with normal immune systems who are infected with *M. tuberculosis* will develop TB disease at some point in their lives (Zumla et al., 2013).

ACTIVE TB INFECTION

TB bacteria become active if a healthy immune system is not present. Active bacteria multiplying in vivo are called TB disease. People with active TB disease are infectious (CDC, 2016b).
LATENT TB VERSUS TB DISEASE

<table>
<thead>
<tr>
<th>A person with latent TB infection . . .</th>
<th>A person with TB disease . . .</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has no symptoms</td>
<td>Has symptoms that may include:</td>
</tr>
<tr>
<td></td>
<td>• A bad cough that lasts 3 weeks or longer</td>
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<tr>
<td></td>
<td>• Pain in the chest</td>
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<td></td>
<td>• Coughing up blood or sputum</td>
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<td></td>
<td>• Weakness or fatigue</td>
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<td></td>
<td>• Weight loss</td>
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<td></td>
<td>• No appetite</td>
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<tr>
<td></td>
<td>• Chills</td>
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<td></td>
<td>• Fever</td>
</tr>
<tr>
<td></td>
<td>• Sweating at night</td>
</tr>
<tr>
<td>Does not feel sick</td>
<td>Usually feels sick</td>
</tr>
<tr>
<td>Cannot spread TB bacteria to others</td>
<td>May spread TB bacteria to others</td>
</tr>
<tr>
<td>Usually has a skin test or blood test result indicating TB infection</td>
<td>Usually has a skin test or blood test result indicating TB infection</td>
</tr>
<tr>
<td>Has a normal chest X-ray and a negative sputum smear</td>
<td>May have an abnormal chest X-ray or positive sputum smear or culture</td>
</tr>
<tr>
<td>Needs pharmacological treatment for latent TB infection to prevent TB disease</td>
<td>Needs pharmacological treatment to treat TB disease</td>
</tr>
</tbody>
</table>

Source: CDC, 2016b.

EXTRAPULMONARY TB

Tuberculosis disease most commonly affects the lungs (pulmonary TB). Patients with pulmonary TB disease usually have a cough and an abnormal chest X-ray and may be infectious.

Tuberculosis disease may also occur outside the lungs (extrapulmonary) in the following ways: as a pleural effusion; in the central nervous, lymphatic, or genitourinary systems; in the bones and joints; or as disseminated disease. Extrapulmonary TB is more common in immunosuppressed individuals and in young children; lymphatic TB and miliary disease are particularly common in immunosuppressed individuals. Extrapulmonary TB is often accompanied by pulmonary TB (CDC, 2013e).

**Miliary TB** is the dissemination of *M. tuberculosis* from the lungs to many other organs via the bloodstream. Under a microscope, the bacteria look like millet seeds. This is prevalent in one third of TB cases. Rarely, miliary TB may appear in a single organ (<5%), in many organs, or throughout the body (>90%). If undiagnosed (up to 50% of cases antemortum), the infection could be fatal. Miliary TB may mimic many other diseases depending on the organ system(s) involved.
Classification by Pathogenesis

The current clinical classification system for TB is based on the pathogenesis of the disease. This classification system allows clinicians to track the development of TB in their patients.

Healthcare providers must comply with state and local laws and regulations requiring the reporting of TB. A patient should not have a Class 5 classification for more than three months. All individuals with Class 3 or Class 5 TB are to be reported promptly to the local or state health department (CDC, 2013e).

<table>
<thead>
<tr>
<th>CLASSIFICATION SYSTEM FOR TUBERCULOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
</tr>
<tr>
<td>-------</td>
</tr>
</tbody>
</table>
| 0 | • No TB exposure  
• Not infected | • No history of exposure  
• Negative reaction to tuberculin skin test or QFT-G (QuantiFERON-TB Gold test) |
| 1 | • TB exposure  
• No evidence of infection | • History of exposure  
• Negative reaction to tuberculin skin test or QFT-G |
| 2 | • TB infection  
• No disease | • Positive reaction to tuberculin skin test or QFT-G  
• Negative bacteriologic studies (if done)  
• No clinical, bacteriologic, or X-ray evidence of active TB |
| 3 | • TB infection  
• Clinically active | • *M. tuberculosis* cultured (if done)  
• Clinical, bacteriologic, or X-ray evidence of current disease |
| 4 | • TB infection  
• Not clinically active | • History of episode(s) of TB or  
• Abnormal but stable X-ray findings  
• Positive reaction to the tuberculin skin test or QFT-G and  
• Negative bacteriologic studies (if done)  
• No clinical or X-ray evidence of current disease |
| 5 | • TB suspected | • Diagnosis pending |

Source: CDC, 2013e.
DIAGNOSIS

Presentation

The signs and symptoms of pulmonary TB may include the following:

- Cough (duration of >3 weeks)
- Chest pain
- Hemoptysis (expectoration of blood or of blood-stained sputum)
- Weakness or fatigue
- Fever
- Chills
- Weight loss
- Radiography showing TB  
  (Campos et al., 2016)

The symptoms may be mild or overlooked for months. This may result in delays seeking healthcare and cause transmission of the infection to others. An actively infected person may transmit the disease to as many as 10 to 15 persons in a year (WHO, 2013).

Symptoms of extrapulmonary TB depend on the site affected. Tuberculosis of the spine may cause pain in the back; TB of the kidney may cause blood in the urine. Extrapulmonary TB should be considered in the differential diagnosis of ill individuals who have systemic symptoms and are at high risk for TB (CDC, 2013e).

Medical History

It is important to ask individuals suspected of having TB about their history of TB exposure, infection, or disease. Clinicians may also contact the local health department for information about whether a patient has received TB treatment in the past. If the treatment regimen was inadequate, or if the patient did not adhere to therapy, TB may recur and may be drug-resistant.

It is also important to consider demographic factors (country of origin, age, gender, ethnic or racial group, occupation) that may increase the patient’s risk for exposure to TB or to drug-resistant TB disease. In addition, clinicians should determine whether the patient has medical conditions, especially HIV infection, that increase the risk for latent TB infection to progress to TB disease. Patients who do not know their current HIV status are referred for HIV counseling and testing.
In addition, conducting a history provides an opportunity to establish rapport with the patient and to highlight important aspects of treatment, such as:

- Benefits of treatment
- Importance of adherence to the treatment regimen
- Possible adverse side effects of the regimen
- Establishment of an optimal follow-up plan

**Physical Exam**

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB, but it can provide valuable information about the patient’s overall condition and other factors that may affect how TB is treated.

Certain manifestations of tuberculosis, such as erythema nodosum, can be diagnosed on the basis of physical examination alone since the cutaneous nodules that extend to the layer of subcutaneous tissue are very distinctive (Bataduwaarachchi & Tissera, 2015).

A physical examination may reveal symptoms of tuberculosis, including persistent cough, hemoptysis, fever, chills, or adventitious breath sounds. In the absence of a physical examination, a patient’s tuberculosis symptoms may be subclinical and go unrecognized for a long time (WHO, 2013).

**TB Testing**

Targeted testing for TB infection is done to identify individuals who are at high risk of developing TB disease and who would benefit from treatment. All testing activities should be accompanied by a plan for follow-up medical evaluation and treatment for individuals with TB infection or TB disease. Individuals with a positive test for TB infection should be evaluated for TB disease and, if disease is ruled out, considered for treatment for LTBI (CDC, 2013a).

In the United States, the two preferred methods for detecting TB infection are the **Mantoux tuberculin skin test (TST)** and the **QuantiFERON-TB Gold test (QFT-G)**. The latter replaced the original QuantiFERON-TB test (QFT) (CDC, 2013a). (See below for details on these tests.)

**WHO SHOULD BE TESTED**

Healthcare providers should identify individuals who are in a high-risk category and test them for TB infection as part of a routine evaluation. Flexibility is needed in defining high-priority groups for testing. The changing epidemiology of TB indicates that groups currently considered high-risk for TB disease or infection may be less so over time, and groups currently not identified as high-risk may come to be so (CDC, 2013b).
High-priority groups can be divided into two categories:

- Individuals at risk for TB exposure or infection
- Individuals at risk for TB disease once infected  
  (CDC, 2013b)

**Individuals at Higher Risk for TB Exposure or Infection**

- Close contacts of people known or suspected to have TB
- Foreign-born individuals, including children, who have immigrated within the last five years from areas that have a high TB incidence or prevalence
- Residents and employees of high-risk congregate settings
- Healthcare workers who serve high-risk clients
- Some medically underserved, low-income populations as defined locally
- High-risk racial or ethnic minority populations defined locally as having an increased prevalence of TB
- Infants, children, and adolescents exposed to adults in high-risk categories
- Individuals who inject illicit drugs or any other locally identified high-risk substance users  
  (CDC, 2013b)

**Individuals at Higher Risk for TB Disease Once Infected**

- Those with human immunodeficiency virus (HIV) infection
- Those who were recently infected with *M. tuberculosis* (within the past two years), particularly infants and very young children
- Male gender
- Obesity
- Smoking
- Those who have medical conditions causing immunosuppression
- Those who inject illicit drugs or other groups of high-risk substance users
- Those who have a history of inadequately treated TB
- Those in close proximity with others who have the infection  
  (Chen et al., 2015)
Healthcare agencies or other facilities must consult with the local health department before starting a testing program for TB infection. This will ensure that adequate provisions are made for the evaluation and treatment of individuals whose test results for TB infection are positive.

There is an increased implementation of the Directly Observed Treatment Short-course (DOTS) intended to cure TB in communities considered high risk with more incidence. Individuals with a positive test for TB infection are evaluated for TB disease and, if disease is ruled out, considered for treatment of LTBI.

For individuals who have a positive test for TB infection but have had TB disease ruled out and are refusing treatment for LTBI, routine follow-up tests for LTBI and chest X-rays are unnecessary. These patients should be instructed to seek medical attention if they experience symptoms and signs suggestive of active TB disease. The global cure rate for active TB is presently 86% with widespread testing and aggressive treatment in high-risk countries (Ali, 2016).

**MANTOUX TUBERCULIN SKIN TEST (TST)**

The Mantoux tuberculin skin test is performed by placing an intradermal injection of 0.1 ml of purified protein derivative (PPD) containing 5 tuberculin units (TU) into the volar surface of the forearm. The injection should be made with a disposable 27-gauge tuberculin syringe, just beneath the surface of the skin, with the needle bevel facing upward. This should produce a wheal 6 mm to 10 mm in diameter. Institutional guidelines regarding precautions for infection control (e.g., use of gloves) should be followed (CDC, 2013a). The reaction to the TST should be read 48 to 72 hours after the injection by a trained healthcare worker.

People from countries that use the BCG vaccine for tuberculosis may exhibit a false-positive response to the Mantoux TST. A similar reaction may occur in those who were previously infected with tuberculosis (CDC, 2013e).
The reaction is read by measuring in millimeters the diameter of induration (palpable raised hardened area) across the forearm. If there is no induration, the result should be recorded as 0 mm. The area of erythema should not be measured, just the induration.

![Reading the Mantoux tuberculin skin test reaction: (left, correct) only the induration is being measured; (right, incorrect) the erythema is being measured. (Source: CDC, 2013e.)](image)

**Interpreting TST Reactions**

Skin test interpretation depends on the measurement of the induration and the individual’s risk of being infected with TB or progression to disease if infected.

**Reactions ≥5 mm.** A TST reaction ≥5 mm of induration is interpreted as a positive result in the following groups:

- HIV-infected individuals
- Recent contacts of someone with TB
- Those with fibrotic changes on chest X-ray consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of >15 mg/day of prednisone for >1 month)

**Reactions ≥10 mm.** A TST reaction ≥10 mm of induration is interpreted as a positive result in individuals who do not meet the preceding criteria but who have other risk factors for TB. These include the following:

- Recent arrivals to the United States (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Individuals with medical conditions that place them at high risk
- Children <4 years of age
- Children and adolescents exposed to adults in high-risk categories

**Reactions ≥15 mm.** A TST reaction ≥15 mm of induration is interpreted as a positive result in all cases.

Guidelines for interpreting tuberculin skin test reactions should also be applied to individuals who may have occupational exposure to TB (e.g., staff of nursing homes, drug treatment centers, and correctional facilities). Thus, the appropriate cutoff for defining a positive reaction depends on the employee’s individual risk factors for TB, including recent TB exposure and the prevalence of TB in the facility. In facilities where the risk of exposure is very low, >15 mm may be an appropriate cutoff for employees with no other risk factors (CDC, 2012a; Zumla et al., 2013).

**False Positives, False Negatives**

The TST is a valuable tool, but it is not perfect. Several factors can lead to false-positive and false-negative skin test reactions.

**False-positive** reaction may be caused by:

- Nontuberculous mycobacteria
- BCG vaccination
- Incorrect interpretation
- Administration of incorrect antigen

**False-negative** reaction may be caused by:

- Cutaneous anergy (inability to react to a skin test)
- Recent TB infection
- Very young age (<6 months old)
- Recent live-virus vaccination (including smallpox)
- Overwhelming TB disease
- Some viral illnesses (e.g., measles, chickenpox)
- Incorrect method of administration
- Too little antigen
- Subcutaneous injection
- Incorrect interpretation

(CDC, 2012a)
QUANTIFERON-TB GOLD TEST (QFT-G)

The QuantiFERON-TB Gold (QFT-G) is a whole-blood test approved for diagnosing both LTBI and TB disease. It does not, however, differentiate LTBI from TB disease, and individuals who have a positive QFT-G result, regardless of symptoms or signs, should be evaluated for TB disease before LTBI is diagnosed (Ali, 2016; CDC, 2012b).

The QFT-G can be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of healthcare workers and others undergoing serial evaluation for *M. tuberculosis* infection. The QFT-G is generally used in place of—not in addition to—the TST (CDC, 2013a). A positive QFT-G result should prompt the same public health and medical interventions as a positive TST result. No reason exists to follow a positive QFT-G result with a TST.

The majority of healthy adults who have negative QFT-G results are unlikely to have *M. tuberculosis* infection and do not require further evaluation. However, for people who have had recent contact with individuals having infectious TB, negative QFT-G results should be confirmed with a repeat test performed 8 to 10 weeks after the end of exposure, as is recommended for a negative TST result. Studies to determine the best time to retest contacts with negative QFT-G results have not been reported. Until more information is available, the timing of QFT-G testing should be the same as that used for the TST (Ali, 2016; CDC, 2012b).

### ADVANTAGES AND DISADVANTAGES OF THE QFT-G

**Advantages**

- It requires a single patient visit to draw a blood sample.
- Results can be available within 24 to 48 hours.
- It does not boost responses measured by subsequent tests, which can happen with tuberculin skin tests (TST).
- It is not subject to reader bias, which can occur with TST.
- It is not affected by prior BCG vaccination.

**Disadvantages/Limitations**

- Blood samples must be processed within 12 hours after collection while white blood cells are still viable.
- There are limited data on its use in children <5 years of age, among individuals recently exposed to *M. tuberculosis*, and in immunocompromised individuals (e.g., impaired immune function caused by HIV/AIDS, current treatment with immunosuppressive drugs, selected hematologic disorders, specific malignancies, diabetes, silicosis, and chronic renal failure).
• Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease its accuracy.
• Limited data exist on the use of QFT-G to determine who is at risk for developing TB disease.
• The expense and possible denial of payment by an insurance company may prohibit the use of this test.

Source: Ali, 2016; CDC, 2012b.

CASE

Roberto presents to the emergency room complaining of weight loss, fatigue, a productive cough for over three weeks, night sweats, and fever with chills. The ER physician orders a QuantiFERON-TB Gold (QFT-G) test, knowing that the results will be available in 24 hours. The nurse draws the ordered blood test and takes it to the laboratory. Roberto is told to return at the same time the following day to receive his test results.

The next day Roberto returns and is told that his results are positive. The ER nurse who discharges Roberto provides literature about TB and informs him that the public health department will be notified about his infection. She also gives him information about a local clinic and instructs Roberto to make a follow-up appointment in one month.

NUCLEIC ACID AMPLIFICATION TEST (NAAT)

NAAT is used to amplify DNA and RNA segments to rapidly identify the microorganisms in a specimen. NAAT can reliably detect *M. tuberculosis* bacteria in specimens in hours as compared to one week or more for culture. This test is also used in the United States when results are needed quickly.

Possible benefits of using NAAT include:

• Earlier laboratory confirmation of TB disease
• Earlier treatment initiation
• Improved patient outcomes
• Interruption of transmission by early diagnosis, respiratory isolation, and appropriate treatment
• Earlier, more efficient use of respiratory isolation
• Earlier initiation of contact investigation
• More effective public health intervention
The CDC recommends that NAAT be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations. This form of testing requires well-trained technical staff and sophisticated equipment but can be performed in many settings.

Clinicians need to interpret all laboratory results in the context of the clinical situation. A single negative NAAT result may not be used as a definitive result to exclude TB disease when the clinical suspicion of TB disease is moderate to high. The negative NAAT result might be used as additional information in making clinical decisions to prevent unnecessary TB disease treatment.

**XPERT MTB/RIF**

A new molecular diagnostic test—the newest of the nucleic acid amplification tests (NAAT)—called Xpert MTB/RIF assay detects *M. tuberculosis* complex within 2 hours with an assay sensitivity that is much higher than that of any other TB test (Zumla et al., 2013). Rapid initiation of treatment is one of the means to reduce the incidence of global TB. Xpert MTB/RIF assay is not prone to contamination and is advocated by some experts in the United States when results are needed more quickly than the Mantoux skin test or the QFT-G test. Its sensitivity is equivalent to solid culture, as much as 99%, and it simultaneously detects rifampicin resistance (Sharma et al., 2015).

**Special Testing Situations**

Special testing situations include those involving pregnant women, live virus vaccination, anergy, boosted reaction, two-step testing, and occupational settings.

**PREGNANT WOMEN**

Tuberculin skin testing (TST) is both safe and reliable to use throughout the course of pregnancy. TB blood testing, while safe, has not been evaluated for diagnosing TB during pregnancy, and other tests are needed for diagnosis (CDC, 2014a).

**LIVE VIRUS VACCINATION**

Vaccination with live viruses (e.g., measles and smallpox viruses) may interfere with TST reactivity and cause false-negative reactions. For individuals scheduled to receive tuberculin skin testing, the testing should be done:

- On the same day as vaccination with live-virus measles vaccine or 4 to 6 weeks after measles vaccination to prevent possible false-positive results
- At least one month after smallpox vaccination (Kroger & Strikas, 2015)
ANERGY

Anergy is the inability to react to a TST because of a weakened immune system. The absence of a reaction to the TST does not rule out the diagnosis of TB infection. Anergy may be caused by many factors, such as HIV infection, severe or febrile illness, measles or other viral infections, Hodgkin disease, sarcoidosis, live-virus vaccination, the administration of corticosteroids or immunosuppressive drugs, and the underdeveloped immune system in young children. The use of anergy testing in conjunction with tuberculin skin testing is not routinely recommended (Ignatavicius & Workman, 2015).

BOOSTED REACTION

In some people who are infected with *M. tuberculosis*, hypersensitivity to tuberculin may wane over the years. When these people are tuberculin skin-tested many years after infection, they may have a negative reaction. However, the skin test itself may stimulate (“boost”) their ability to react to tuberculin, causing a positive reaction in subsequent tests. This boosted reaction can be misinterpreted as a new infection. The booster phenomenon may occur at any age; its prevalence increases with age and it is highest among older adults. Boosted reactions may occur in individuals infected with nontuberculous mycobacteria or in individuals who have had a BCG vaccination (CDC, 2012a).

TWO-STEP TESTING

Two-step testing is a strategy used to reduce the likelihood that a boosted reaction (due to infection in the past or recent TST) will be misinterpreted as a recent infection.

If the reaction to the first test is classified as negative, a second test is repeated one to three weeks later. A positive reaction to the second test probably represents a boosted reaction. On the basis of this second test result, the person is classified as previously infected. This is not considered a skin test conversion or a new TB infection; however, the patient may still be a candidate for LTBI treatment. If the second test result is also negative, the person is classified as having a negative baseline TST result (CDC, 2013d).
OCCUPATIONAL SETTINGS

High-risk congregate facilities, especially healthcare facilities, are settings where there is a high risk of TB transmission. Examples may include correctional facilities, nursing homes, homeless shelters, hospitals, residential facilities for individuals living with AIDS, and other healthcare facilities.

Residents and employees of high-risk congregate facilities are tested for TB upon employment or entry into the facility and thereafter at intervals determined by the risk of transmission in that facility. Diagnosis is made by conversion of the tuberculin skin test, DNA genotyping techniques, and contact investigations. This testing is done for two reasons:

- To detect TB infection or disease in staff or residents so that they may be treated
- To survey TB transmission in the facility

(Pedersen et al., 2016)
Chest Radiography

A posterior-anterior X-ray of the chest is the standard view used for the detection and description of chest abnormalities. In some instances, other views (e.g., lateral, lordotic) or additional studies (e.g., CT scans) may be necessary. The cavitation indicated by the arrows in the image below is suggestive of pulmonary tuberculosis but does not definitively diagnose the disease. A suspicious chest X-ray may be followed by computerized tomography (CT) of the chest to better view the suspected cavitation (CDC, 2013e).

![Chest radiograph with lower lobe cavity suggestive of pulmonary TB.](Source: CDC, 2013e.)

Diagnostic Microbiology

Individuals suspected of having pulmonary or laryngeal TB need at least three sputum specimens examined by acid-fast bacilli (AFB) smear and culture. Detection of AFB in stained smears examined microscopically may provide the first bacteriologic clue of the existence of TB.

**ZIEHL-NEELSON STAINING/ACID-FAST BACILLUS**

The Ziehl-Neelson staining procedure, introduced in the 1890s, was named for its two German developers. This method relies on the “acid-fast” characteristic (resistance to decolorization by acids during staining) of *M. tuberculosis* and is thus also referred to as an AFB (acid-fast bacilli) smear and culture. It remains in use today as a way to diagnose TB.
However, smear examination permits only the presumptive diagnosis of TB because the AFB in a smear may be acid-fast organisms other than *M. tuberculosis*. Furthermore, many TB patients have negative AFB smears.

Positive cultures for *M. tuberculosis* confirm the diagnosis of TB; however, TB may also be diagnosed on the basis of clinical signs and symptoms in the absence of a positive culture. Culture examinations for the purpose of diagnosis are performed on all specimens regardless of AFB smear results (Ignatavicius & Workman, 2015).

Acid-fast microscopy cultures can be performed quickly (within 24 hours, one hour if urgent), assess the response to treatment, and are inexpensive (Datta et al., 2015).

For all patients, the initial *M. tuberculosis* isolate is tested for resistance to the first-line antituberculosis medications. Drug-susceptibility testing is not widely available in regions in which tuberculosis is endemic (emerging countries), particularly for second-line drugs. It is crucial to identify drug resistance as early as possible in order to ensure appropriate treatment (Zumla et al., 2013).

**REPORTING POSITIVE CULTURES**

Laboratories should report initial positive smears and positive *M. tuberculosis* cultures within 24 hours to the primary healthcare provider. Out-of-state laboratories that receive referral specimens must contact the healthcare provider in the patient’s state of origin. It is the responsibility of the primary healthcare provider to promptly report all suspected or confirmed cases of TB to the state or local health department so that a contact investigation can be initiated quickly to interrupt the potential ongoing transmission.

Each jurisdiction maintains its own policies for conveying this information. For example, Los Angeles County allows reporting to be done via mail, telephone, fax, or by courier, as these methods are considered safe enough not to violate patient privacy (County of Los Angeles Public Health, 2016a).
TREATING LATENT TUBERCULOSIS INFECTION (LTBI)

For more than 90% of persons infected with *M. tuberculosis*, the pathogen is contained as asymptomatic latent infection. The risk of active disease is approximately 5% in the 18 months after initial infection and approximately 5% for the remaining lifetime. An estimated 2 billion persons worldwide have latent infection and are at risk for activation (Ali, 2016; Zumla et al, 2013).

Treatment of latent tuberculosis infection is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease.

Careful assessment to rule out the possibility of TB disease is necessary before treatment for LTBI is started. There are several regimens available for the treatment of LTBI, and providers need to discuss these treatment options with their patients. Isoniazid may be given over a 3-month period or rifampin may be given for a shorter amount of time. The shorter duration of treatment may improve patient compliance (Turetz & Ma, 2016).

Target Testing

Certain groups are at very high risk for developing TB disease once infected. Targeted testing programs are designed to identify individuals who are at high risk for TB and who would benefit from treatment of LTBI.

<table>
<thead>
<tr>
<th>FACTORS INCREASING RISK THAT LTBI WILL PROGRESS TO TB DISEASE</th>
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<tbody>
<tr>
<td>Conditions that increase the risk that latent TB infection will progress to TB disease include:</td>
</tr>
<tr>
<td>• Human immunodeficiency virus (HIV) infection</td>
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<tr>
<td>• Previous TB (in an individual who received inadequate or no treatment) indicated by chest X-ray</td>
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<tr>
<td>• Prolonged corticosteroid therapy and other immunosuppressive therapy</td>
</tr>
<tr>
<td>• Recent infection with <em>M. tuberculosis</em> (within the past two years)</td>
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<tr>
<td>• Substance abuse (especially intravenous drug use)</td>
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<td>• Silicosis</td>
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<tr>
<td>• Diabetes mellitus</td>
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<tr>
<td>• End-stage renal disease</td>
</tr>
<tr>
<td>• Cancer of the head and neck</td>
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</tbody>
</table>
• Hematologic and reticuloendothelial diseases
• Intestinal bypass or gastrectomy
• Chronic malabsorption syndromes (e.g., Crohn’s disease)
• Low body weight (10% or more below ideal) (CDC, 2016a)

The risk may be approximately three times greater (e.g., diabetes) to more than 100 times greater (e.g., HIV infection) for individuals who have these conditions than for those who do not. HIV infection is the strongest known risk factor for development of TB disease in individuals with LTBI. The risk of developing TB is 7% to 10% each year for those who are infected with both *M. tuberculosis* and HIV, whereas it is 10% over a lifetime for those infected only with *M. tuberculosis*.

In general, individuals with no known risk factors for TB are not tested for LTBI. However, testing is occasionally performed among certain population groups for surveillance purposes or where cases of active TB may result in extensive transmission. If testing is performed in these populations, they may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥10 mm of induration (Asl et al., 2015).

Some close contacts who have a negative tuberculin skin test reaction (<5 mm of induration) should be evaluated for treatment of LTBI. Treatment for LTBI is begun after TB disease has been ruled out. These contacts include children <4 years of age, immunosuppressed people, and others who may develop TB disease quickly after infection.

Close contacts that have a negative reaction to an initial skin test are retested 10–12 weeks after they were last exposed to TB. Treatment may be discontinued if the skin test result is again negative and if the individual is no longer exposed to TB. However, close contacts known to have or suspected of having HIV infection and other immunocompromised individuals are treated for LTBI regardless of their skin test reaction.

Because of their age, infants and young children with a positive skin test must have been infected recently and are known to be at high risk of their infection progressing to disease. Infants and young children are also more likely than older children and adults to develop life-threatening forms of TB disease.

Children <4 years of age who are close contacts to someone with infectious TB need treatment for LTBI even if the tuberculin skin test result and chest X-ray do not suggest TB. A second tuberculin test should be placed 10 to 12 weeks after the last exposure to infectious TB. Treatment of LTBI can be discontinued at that time if all of the following conditions are met:

• The second tuberculin test is negative
• The second test was performed at least 10 weeks after the child was last exposed to infectious TB
• The child is at least six months of age (CDC, 2013h)

Treatment Regimens

Healthcare providers need to discuss treatment options with their patients. Providers acting in a case management or similar capacity who are not the primary determiners of a patient’s regimen should still be fully versed in drug basics, components of the regimen, proper dosing instructions, adverse reactions, and all other relevant information. Treatment of LTBI can be complex and lengthy; a fully informed healthcare provider will greatly aid patient understanding, which in turn will facilitate compliance and recovery.

For individuals who are at especially high risk for TB, are on an intermittent dosing regimen, or are at risk for nonadherence, directly observed therapy (DOT) of LTBI should be considered. Multiple studies show improved compliance and better outcomes when drug therapy is supervised either in the home or healthcare settings. This method of treatment is especially appropriate when a household member is on DOT for active disease or in institutions and facilities where a staff member can observe infection treatment. In some instances, maintaining compliance can be difficult when access to the facility where treatment takes place is a barrier (Yin et al., 2016).

DIRECTLY OBSERVED THERAPY (DOT)

DOT means that a nurse or another designated individual watches the patient swallow each dose of TB medication. DOT can significantly reduce the development of drug resistance, treatment failure, or relapse after treatment ends. Establishing a relationship with the patient and addressing barriers to adherence is the core of a successful DOT program.

It is important that DOT be carried out at times and in locations that are as convenient as possible for the patient. Therapy may be directly observed in a medical office or clinic setting but can also be observed by an outreach worker in the field. In some situations, staff in correctional facilities or drug treatment programs, home healthcare workers, maternal and child health staff, or designated community members may provide DOT.

DOT is recommended for all children and adolescents with TB. Even when drugs are given under DOT, tolerance to the medications must be monitored closely. It is not advised to rely on parents alone to supervise DOT (Yin et al., 2016).

CURRENT TREATMENT GUIDELINES

Isoniazid (INH) is normally used alone for treatment of LTBI. Isoniazid can be given daily or two times a week (as DOT).
Suggested treatment regimens for LTBI include the following:

- A 9-month regimen of isoniazid is considered optimal treatment for both HIV-infected and HIV-negative adults.
- A 4-month regimen of daily rifampin (RIF) (Rifadin) is an alternative option, and for individuals known to be contacts of patients with INH-resistant, RIF-susceptible TB.
- The 2-month regimen of rifaximin (Xifaxan) and pyrazinamide (PZA) should generally not be used due to an increased risk of severe liver injury and death.
- For individuals likely to have been infected with a strain of *M. tuberculosis* that is resistant to both isoniazid and rifampin (Rifadin), alternative regimens considered should consist of drug(s) to which the infecting organism has demonstrated susceptibility.

For individuals suspected of having LTBI, treatment should not begin until active TB disease has been excluded by history, physical examination, chest X-ray, and when indicated, bacteriologic studies. When isoniazid is given alone to individuals with active TB disease, resistance to the drug is more likely to develop. For this reason, individuals suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Treatment of LTBI for six months rather than nine months may be more cost-effective and result in greater adherence by patients; therefore, local TB programs may prefer to implement the six-month regimen. The six-month regimen is not recommended for children, HIV-infected individuals, or those with stable fibrotic lesions seen on chest X-ray that are consistent with prior TB (CDC, 2013d).

### RECOMMENDED DRUGS FOR LATENT TB INFECTION

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH), 300 mg maximum, daily for at least 6 months, and preferably for 9 months</td>
<td>Recommended for 9 months or more in HIV-infected patients; daily administration for 6 months is also an option, but with lower efficacy. Extension to 36 months further reduces risk among HIV-positive patients in regions in which tuberculosis is endemic.</td>
</tr>
<tr>
<td>Isoniazid, 900 mg, plus rifapentine (Priftin), 900 mg, weekly for 3 months (DOT)</td>
<td>Studied with DOT in predominantly HIV-uninfected persons; higher completion rates and equal efficacy, as compared with isoniazid for 9 months.</td>
</tr>
<tr>
<td>Rifampin (Rifadin), 600 mg, daily for 4 months</td>
<td>Shown to be effective in persons with silicosis.</td>
</tr>
<tr>
<td>Isoniazid, 300 mg, plus rifampin (Rifadin), 600 mg, daily for 3 months</td>
<td>Effective alternative for HIV-infected patients.</td>
</tr>
<tr>
<td>Isoniazid, 900 mg, plus rifampin (Rifadin), 600 mg, twice weekly for 3 months</td>
<td>Another effective alternative for HIV-infected persons.</td>
</tr>
</tbody>
</table>

Source: Vallerand et al., 2015; Zumla et al., 2013.
ADJUSTED TREATMENT REGIMENS

The following individuals or situations may require adjusted treatment regimens, in consultation with appropriate healthcare providers and/or LTBI/TB experts:

- Contacts of isoniazid-resistant TB
- Contacts of multidrug-resistant TB
- Immunocompromised contacts
- Individuals with fibrotic lesions
- Women who are pregnant or breastfeeding

For patients who are pregnant and at high risk for progression of LTBI to active disease (e.g., HIV-positive or recently infected), initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. Careful clinical and laboratory monitoring for hepatitis is indicated (CDC, 2013d).

Breastfeeding is not contraindicated when a mother is being treated for LTBI. Likewise, the amount of isoniazid provided in breast milk is inadequate for the treatment of an infant. Infants whose breastfeeding mothers are taking isoniazid should receive supplemental pyridoxine (CDC, 2013c).

EMERGING TREATMENT OPTION

The recently completed PREVENT TB study, sponsored by CDC, was one of the largest U.S. government clinical trials conducted to date on latent TB treatment. The results represent one of the most significant advances in TB research in decades. The trial lasted approximately 10 years and enrolled more than 8,000 participants, mostly in the United States and Canada.

While the current standard treatment regimen consists of a self-administered daily dose of isoniazid taken for 9 months, the study treatment regimen consisted of a once-weekly dose of rifapentine (Priftin) and isoniazid administered by DOT for 3 months and a total of 12 doses.

The outcome of the trial represents a major advance in TB treatment:

- The new regimen is simpler, reducing the required treatment from 270 daily doses over 9 months to 12 once-weekly doses over 3 months.
- The study results suggest that LTBI can be treated more easily, which may prevent more cases and slow the spread of TB disease.
- The trial results are applicable only to countries with low-to-medium TB incidence. Additional research will likely be needed before the new regimen can be recommended in countries with a high incidence of TB or in certain sectors of the United States. Health departments must decide what treatment regimen for LTBI is best.
• The CDC recently convened an expert consultation to review the data and begin working on new treatment guidelines for the use of the new regimen in the United States. These guidelines can be found on the CDC website (see “Resources” at the end of this course).

The newer, easier 12-dose treatment regimen for latent TB is now recommended for use under directly observed therapy (DOT) standards (CDC, 2013f; Cruz & Stark, 2016). More recent studies show that the original work done in the landmark PREVENT TB study show the original research has been replicated, including in the pediatric population, and the 12-dose, once-weekly isoniazid/rifapentine (3HP) regimen continues to show better compliance and cost-effectiveness (Cruz & Starke, 2016).

Baseline and Routine Laboratory Testing

Recommendations for laboratory testing vary according to the patient:

• Baseline laboratory testing is not routinely indicated for all patients at the start of LTBI treatment.

• Baseline and monthly hepatic measurements of serum aminotransferase and bilirubin are indicated for patients using isoniazid (INH). (Active hepatitis and end-stage liver disease are relative contraindications to the use of INH.)

• Baseline testing is also indicated for patients with HIV infection, women who are pregnant or in the immediate postpartum period, individuals with a history of liver disease, individuals who use alcohol regularly, and others who are at risk for chronic liver disease.

• Baseline laboratory testing is not routinely indicated in older adults. However, testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions.

• Routine laboratory monitoring during treatment of LTBI with rifampin (Rifadin) is indicated by periodic evaluation of renal function, CBC, and urinalysis to allow for the evaluation of possible adverse reactions that might occur during treatment. (Vallerand et al., 2015)

Monthly Evaluations

During treatment of LTBI, patients should be clinically evaluated at least once a month for:

• Adherence to the prescribed regimen
• Signs and symptoms of active TB disease
• Signs and symptoms of hepatitis

Patients should be instructed to stop taking medication immediately and seek medical consultation if abdominal pain, emesis, jaundice, or other hepatitis symptoms develop.
TREATMENT OF TB DISEASE

Tuberculosis disease must be treated over a long period of time compared to many other infectious diseases. If treatment is not continued for a sufficient length of time, some tubercle bacilli may survive and the patient may become ill and infectious again.

The principles for the treatment of tuberculosis are to:

- Cure the patient and restore health, quality of life, and productivity
- Prevent death from active TB or its complications
- Prevent relapse of TB
- Reduce transmission of TB to others, especially those closest to the patient
- Prevent the development of acquired drug resistance

(DOH RSA, 2014)

Tuberculosis treatment regimens must contain multiple drugs to which the organisms are susceptible. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug. Likewise, the addition of a single drug to a failing antituberculosis regimen can lead to drug resistance (Zumla et al., 2013).

For each patient with newly diagnosed TB, a specific treatment and monitoring plan should be developed. This plan includes immediate initiation of combination drug therapy and should include a description of the treatment regimen, the methods of assessing and ensuring adherence to the antituberculosis regimen, and the methods of monitoring for adverse reactions. Health teaching may include nutritional counseling, smoking cessation, Alcoholics or Narcotics Anonymous (if needed), and at least one year of follow up medical care (Ignatavicius & Workman, 2015).

Treatment Regimens

As of 2016, there are 10 drugs approved by the U.S. Food and Drug Administration for treating TB. Of the approved drugs, isoniazid (INH), rifampin (Rifadin), ethambutol (Myambutol), and pyrazinamide (PZA) are considered first-line antituberculosis agents, forming the core of initial treatment regimens (CDC, 2016c).

### RECOMMENDED DRUGS FOR ACTIVE TB

<table>
<thead>
<tr>
<th>Active TB Disease (newly diagnosed cases that are not multidrug-resistant)</th>
<th>Recommended Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Regimen</td>
<td>Isoniazid (INH), rifampin (Rifadin), ethambutol (Myambutol), and pyrazinamide (PZA) for 2 months (intensive phase); followed by isoniazid and rifampin (Rifadin) for 4 months (continuation phase)</td>
<td>Pyridoxine supplementation is recommended to prevent isoniazid-induced neuropathy.</td>
</tr>
</tbody>
</table>

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### Active TB Disease (multidrug-resistant)

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Four second-line antituberculosis drugs (as well as pyrazinamide [PZA]), including: 1) a fluoroquinolone; 2) a parenteral agent; 3) ethionamide (Trecator) or prothionamide; and 4) either cycloserine (Seromycin), or if this is contraindicated, para-aminosalicylic acid (Paser)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Initial treatment is based on local disease patterns and pending drug-susceptibility results; later-generation fluoroquinolones (e.g., moxifloxacin [Avelox] or levofloxacin [Levaquin]) are preferred.</td>
</tr>
</tbody>
</table>

Source: Zumla et al., 2013.

### RECOMMENDED DRUG DOSES FOR TB DISEASE TREATMENT

#### Isoniazid (INH)
- Dose: 4–6 mg/kg
- Daily maximum: 300 mg
- 3x/wk dosing: 8–12 mg/kg
- 3x/wk daily maximum: 900 mg

#### Rifampin (RIF)
- Dose: 8–12 mg/kg
- Daily maximum: 600 mg
- 3x/wk dosing: 8–12 mg/kg
- 3x/wk daily maximum: 600 mg

#### Pyrazinamide (PZA)
- Dose: 20–30 mg/kg
- 3x/wk dosing: 30–40 mg/kg

#### Ethambutol (EMB)
- Dose: 15–20 mg/kg
- 3x/wk dosing: 25–35 mg/kg

#### Streptomycin*
- Dose: 12–18 mg/kg
- 3x/wk dosing: 12–18 mg/kg
- 3x/wk daily maximum: 1000 mg

* Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in patients in this age group. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily.

Source: Source: CDC, 2016c.
PULMONARY TB

There are four regimens recommended for treating adults with culture-positive TB caused by organisms known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial two-month treatment phase followed by a continuation phase. The continuation phase is generally four months, although the continuation phase should be extended to seven months (an additional three months) for people with weakened immune systems.

All TB drugs should be given together rather than in divided doses. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances.

Treatment completion is defined primarily by the number of doses ingested within a specified time period. The duration of therapy depends on the drugs used, the drug susceptibility test results, and the patient’s response to therapy. Most patients with previously untreated pulmonary TB can be treated with either a six-month or nine-month regimen, although the six-month regimen is preferred. All six-month regimens must contain INH, RIF, and initially, PZA; all regimens of nine months or less must contain INH and RIF (CDC, 2016c).

Interruptions in the treatment of TB are common. Healthcare providers are responsible for deciding whether to restart a complete course of treatment or to continue as originally planned. These decisions should be based on when the interruption occurred and the duration of the interruption. A common occurrence in the prolonged course of drug therapy is poor patient compliance. Inadequate drug treatment may have the following outcomes:

- Prolonged illness and disability for the patient
- Infectiousness of the patient causing continued TB transmission in the community
- Development of drug-resistant TB
- The possibility of death
  (DOH RSA, 2014)

_Treating HIV-Positive Individuals_

A major concern in treating TB in the setting of HIV infection is the interaction of RIF with antiretroviral agents. Antiretroviral therapy should not be withheld because the patient is being treated for TB. However, it is not advisable to begin both antiretroviral therapy and combination chemotherapy for TB at the same time (CDC, 2013e).

_Treatment During Pregnancy and Breastfeeding in Women_

Women of childbearing age should be asked about pregnancy status before starting TB treatment. Untreated TB represents a greater hazard to a pregnant woman and her fetus than does treatment of the disease. Treatment of a pregnant woman with suspected TB should be started if the probability of TB is moderate to high. Rarely, a baby may be born with TB (CDC, 2013c).
In general, administration of antituberculosis drugs is not an indication for termination of pregnancy. However, in women who are being treated for drug-resistant TB, counseling concerning the risk to the fetus for congenital defects and fetal demise should be provided because of the known and unknown risks of the second-line antituberculosis drugs. Possible risks may include congenital defects, placental vasoconstriction, preterm labor, and fetal hypoxia.

Timely and properly applied chemotherapy is the best way to prevent transmission of tuberculosis to the baby. After active TB in the baby is ruled out, the baby should be given six months of isoniazid preventive therapy, followed by BCG vaccination (Gunatilake & Patil, 2016).

Breastfeeding should not be discouraged for women being treated with first-line antituberculosis drugs because the small concentrations of these drugs in breast milk do not produce toxic effects in the nursing infant. Conversely, drugs in breast milk should not be considered to serve as effective treatment for active TB or latent TB infection in a nursing infant.

Supplementary pyridoxine (vitamin B6) is recommended both for the nursing mother and her infant. Due to the potential ototoxicity to the newborn, the administration of fluoroquinolones during breastfeeding is not recommended (CDC, 2013c).

**Treating Children and Adolescents**

In the United States, 9,582 cases of TB were reported in 2013, 5% of which were children under 15 years old. The worldwide estimate is of at least one million cases of TB among children under 15 years old. In high TB-burden settings outside of the United States, it is estimated that 15% to 20% of TB cases are children. Infants and young children are more likely than adults and older children to develop life-threatening forms of TB such as disseminated TB and TB meningitis.

A pediatric TB specialist should be consulted to ensure appropriate treatment parameters. The lack of pediatric dosage forms of most antituberculosis medications may necessitate using crushed pills and suspensions, and drug regimens will need to be adjusted for children. It is essential that children (and anyone being treated for TB) take the medications exactly as directed and finish the entire course of treatment (CDC, 2016d).

**Treating Patients with Renal Insufficiency and Liver Disease**

Medical conditions that require additional treatment considerations include renal insufficiency or end-stage renal disease and hepatic disease.

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is two months of isoniazid (INH), rifampin (Rifadin), pyrazinamide (PZA), and ethambutol (Myambutol), followed by four months of isoniazid and rifampicin (Rifadin). Isoniazid and rifampin (Rifadin) are eliminated by biliary excretion;
therefore no change in dosing is necessary. In severe renal failure, patients are given pyridoxine with isoniazid to prevent peripheral neuropathy.

Isoniazid, rifampicin, and pyrazinamide are all minimally associated with hepatocellular damage. In patients with unstable or advanced liver disease, baseline liver function tests are checked at the start of treatment. Expert consultation is essential in treating patients with unstable or advanced liver disease. Patients with TB and any chronic liver disease should not receive pyrazinamide (DOH RSA, 2014).

EXTRAPULMONARY TB

As a general rule, principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. Pulmonary and extrapulmonary disease should usually be treated with the same regimens. For patients with TB in the bones/joints or miliary TB, treatment may need to be extended to nine months (DOH RSA, 2014).

DRUG-RESISTANT TB

Tuberculosis that is resistant to at least two of the best anti-TB drugs—isoniazid and rifampin (Rifadin)—is called multidrug-resistant TB (MDR-TB). Because these drugs are considered first-line drugs, they are used to treat all persons with TB disease. Pharmacologic treatment of MDR-TB cost approximately 10 times that of drug-sensitive TB (Potter et al., 2014).

Formally considered as one of the second lines of defense, fluoroquinolone antibacterial drugs for tuberculosis are used only if there is no other option since those drugs have side effects that may outweigh their benefits.

There are two types of drug resistance: primary and secondary. Primary resistance develops in individuals who are initially infected with resistant organisms. Secondary resistance, or acquired resistance, develops during TB therapy either because the patient was treated with an inadequate regimen or because the patient did not take the prescribed regimen appropriately.

Patients at increased risk for drug resistance include those with:

- Cultures that remain positive despite two months of therapy with TB drugs
- Inadequate treatment regimens for >2 weeks
- A history of treatment with TB drugs
- Contact with an individual known to have drug-resistant TB
- Ethnic origin from foreign areas where the prevalence of drug-resistant TB is high (CDC, 2016e)

A group of U.S. scientists at the Southern Research Institute developed a multifunctional molecule called Compound 2 while performing research to develop a new HIV antiretroviral
drug. Compound 2 interacts with first-line TB drugs to act as an anti-MDR-TB agent and allow these drugs to be more effective (Nair et al., 2015).

Recent studies found that combining intravenous infusions of the carbapenem category of antibiotics with oral dosages of β-lactam antibiotics such as amoxicillin-clavulanic acid reduced the sputum mycobacterial load by 1.5 orders of magnitude compared to the use of more traditional antituberculosis drugs such as isoniazid, rifampin, pyrazinamide, and ethambutol. The study results promise the possibility of a more effective drug regime for MDR-TB (Diacom et al., 2016).

**Extensively drug-resistant TB** (XDR TB) is a relatively rare type of MDR-TB. XDR TB is defined as TB that is resistant to isoniazid and rifampin (Rifadin), plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs, i.e., amikacin (Amikin), kanamycin (Kantrex), or capreomycin (Capastat). Because XDR TB is resistant to first-line and second-line drugs, patients may be left with treatment options that are much less effective.

XDR TB is a concern for persons with HIV infection or other conditions that can weaken the immune system. These persons are more likely to develop TB disease once they are infected and have a higher risk of death once they develop TB.

In a patient with newly diagnosed TB, drug resistance is suspected if the patient was previously treated for TB, did not complete a prescribed TB treatment regimen, had contact with a known drug-resistant case, or spent time in a region in which drug resistance is very common. Drug resistance is confirmed only by drug-susceptibility testing.

Patients with strains of *M. tuberculosis* that are resistant to both isoniazid and rifampin (MDR-TB) are at high risk for treatment failure and further acquired resistance (CDC, 2016e).

**Patient Monitoring**

Clinicians who treat TB must be familiar with the methods of monitoring for adverse reactions and treatment responses among patients. All patients need to be monitored to assess their response to therapy and compliance. In some situations (drug-resistant TB, pregnancy, HIV-positive patients), expert consultation may be required.

**BASELINE MONITORING**

When TB treatment is initiated, the following examinations are conducted:

- Serologic testing for people at risk for hepatitis B or C (e.g., injection drug use, birth in Asia or Africa, HIV infection)
- Measurement of aminotransferases, bilirubin, alkaline phosphatase, serum creatinine, and a platelet count for all patients
• Testing of visual acuity (Snellen chart) and color vision (Ishihara) when ethambutol (Myambutol) is used
• Measurement of a CD4+ lymphocyte count for HIV-positive individuals (CDC, 2013c)

MONITORING DURING TREATMENT

Patients need clinical evaluations at least monthly to identify possible adverse reactions to medications and to assess adherence. A patient’s weight is monitored monthly, and dosages are adjusted according to weight changes. Patients who have stable abnormalities of hepatic or renal function at baseline need repeat measurements early in the course of their treatment, then less frequently, to ensure the damage has not worsened.

BASELINE AND ROUTINE MONITORING RECOMMENDATIONS

Baseline tests and ongoing monitoring recommendations for adverse effects monitoring include:

• Blood tests
• Audiology (due to possible ototoxology)
• Visual acuity and color discrimination testing (see below)
• ECG

Monthly testing of visual acuity and color vision is recommended for patients receiving an ethambutol (Myambutol) dose exceeding 15–20 mg/kg (the recommended range) and for patients receiving the drug for more than two months. Patients receiving ethambutol are also questioned monthly regarding visual disturbances. Patients are educated regarding the possible visual side effects of ethambutol and should be instructed to immediately report vision changes to their healthcare provider (Vallerand et al., 2015).

For patients with extrapulmonary TB, clinical monitoring is the usual way of assessing the response to treatment. The frequency and kinds of evaluations will depend on the sites involved and the ease with which specimens can be obtained.

MICROBIOLOGIC MONITORING

For a patient whose sputum culture is positive before treatment, sputum smear microscopy is performed at completion of the intensive phase of treatment and repeated monthly if the sputum smear continues to be positive, until two consecutive cultures are negative (CDC, 2012n). Sputum specimens are collected for smear examination during each follow-up sputum check. They should be collected without interrupting treatment and transported to the laboratory as soon as possible thereafter. Patients whose sputum no longer contains *M. tuberculosis* after two
months of treatment need at least one additional sputum smear and culture performed at the completion of therapy (WHO, 2013).

Patients with MDR-TB require sputum cultures performed monthly for the entire course of their treatment and after the cultures are negative (CDC, 2013h).

It is unnecessary, unreliable, and a waste of resources to monitor the patient undergoing TB treatment by chest radiography since pulmonary abnormalities will not improve right away; instead, a follow-up chest X-ray is done after completion of the drug regime (WHO, 2013). The intervals at which chest radiography should be repeated will depend on the patient’s symptoms and the differential diagnosis that is being considered. Sputum cultures are the leading means to monitor the effectiveness of a TB treatment regimen (CDC, 2013e).

Important treatment decisions concerning the continuation phase regimen are based on the patient’s microbiologic status at the end of the initial phase of treatment (i.e., at two months). The continuation phase is extended to 28 weeks if a patient has a positive sputum culture after two months of therapy and has cavitation on the initial chest X-ray. Patients whose cultures remain positive or whose symptoms do not resolve despite three months of therapy are reevaluated for potential drug-resistant disease as well as for potential failure to adhere to the regimen (CDC, 2013e).

A positive sputum smear at the end of the intensive phase may indicate any of the following:

- The initial phase of therapy was poorly supervised and patient adherence was poor.
- The anti-TB drugs were of poor quality.
- The doses of anti-TB drugs were below the recommended range.
- Resolution is slow because the patient had extensive cavitation on chest X-ray and a heavy initial bacteria count.
- There are comorbid conditions that interfere either with adherence or with response.
- The patient may have drug-resistant TB that is not responding to first-line treatment.
- Nonviable bacteria remain visible by microscopy. (WHO, 2013)

**MONITORING FOR ADVERSE REACTIONS**

In addition to microbiologic evaluations, it is essential that patients have clinical evaluations to identify possible adverse effects to the antituberculosis medications. Monitoring for adverse reactions must be individualized. The type and frequency of monitoring depends on the drugs used and the patient’s risk for adverse reactions (e.g., age, alcohol use). At minimum on a monthly basis during therapy, healthcare providers should examine patients and interview them concerning any adverse reactions even if no problems are apparent.
Adverse reactions to TB drugs are relatively rare, but in some patients they may be severe. Mild adverse effects can generally be managed with symptomatic therapy. The drug or drugs must be discontinued if there are more severe effects. It is important that first-line drugs not be stopped without adequate justification. Proper management of serious adverse reactions often requires expert consultation.

Patients are specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking. They are also instructed to seek medical attention immediately should these symptoms occur. All patients receiving INH, RIF, or PZA should be instructed to stop taking the medications and to immediately report any symptoms suggestive of hepatitis. If the symptoms suggest adverse reactions, appropriate laboratory testing is performed (CDC, 2013d).

### COMMON ADVERSE REACTIONS TO TB DRUGS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Reaction*</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>Allergic</td>
<td>Skin rash</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Eye damage</td>
<td>Blurred or changed vision; changed color vision</td>
</tr>
<tr>
<td>Isoniazid, Pyrazinamide, Rifampin</td>
<td>Hepatitis</td>
<td>Abdominal pain, abnormal liver function test results, dark urine, fatigue, fever for 3 or more days, flu-like symptoms, lack of appetite, nausea, vomiting, yellowish skin or eyes</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Nervous system damage</td>
<td>Dizziness, tingling, or numbness around the mouth</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Tingling sensation in hands and feet</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Stomach upset</td>
<td>Stomach upset, vomiting, lack of appetite</td>
</tr>
<tr>
<td></td>
<td>Increased uric acid</td>
<td>Abnormal uric acid level, joint aches, gout (rare)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Bleeding problems</td>
<td>Easy bruising, slow blood clotting</td>
</tr>
<tr>
<td></td>
<td>Discoloration of body fluids</td>
<td>Orange urine, sweat, or tears; permanently stained soft contact lenses</td>
</tr>
<tr>
<td></td>
<td>Drug interactions</td>
<td>Interference with certain medications, such as birth control pills, birth control implants, and methadone treatment</td>
</tr>
<tr>
<td></td>
<td>Sensitivity to the sun</td>
<td>Frequent sunburn</td>
</tr>
</tbody>
</table>

* For serious adverse reactions, patients should stop taking the medication and consult a clinician immediately. Patients can continue taking medication if they have minor adverse reactions.

Source: CDC 2013e.

### FOLLOW-UP AFTER TREATMENT

Routine follow-up after treatment is not necessary for patients who have had a satisfactory response to a six- or nine-month regimen with both isoniazid and rifampin. Patients whose
organisms were fully susceptible to the drugs being used are instructed to report promptly the development of any symptoms, particularly prolonged cough, fever, or weight loss. For patients with organisms resistant to isoniazid (INH) or rifampin (Rifamid) or both, follow-up evaluation must be individualized (WHO, 2013).

New Drugs

Five new classes of drugs are being investigated in clinical trials. Of these drugs, two classes (nitroimidazoles and oxazolidinones) and two drugs (bedaquiline and SQ-109) have new mechanisms of action for tuberculosis. Phase 2 trials of bedaquiline or delamanid added to current, background therapy for MDR-TB showed a significant increase in the rate of sputum-culture conversion to negative at eight weeks of treatment (Zumla et al, 2013).

The development of new TB drugs has the benefit of providing effective treatment against the disease as the patient becomes progressively more resistant to older drug therapies. Another advantage is that bedaquiline can potentially shorten the duration of treatment.

Bedaquiline is the first new anti-TB drug approved (conditionally) by the FDA in 40 years and has been shown to be an effective treatment option for MDR-TB infection. Delamanid received conditional authorization for marketing by the European Medicines Agency in April 2014 (TBFacts.org, 2016; Cox et al., 2015).

The following table shows the newest TB drugs to be developed and the phase of clinical trials the drugs are in (as of 2016) as they are tested on humans. The drugs in Phase III are the closest to being marketed.

<table>
<thead>
<tr>
<th>Phase of Trials</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>• Q203-Novel anti-TB agent Imidazopyridine</td>
</tr>
</tbody>
</table>
| II              | • Sutezolid (PNU-100480) Oxazolidinone  
               | • SQ109 Ethylenediamine  
               | • Rifapentine for DS-TB Rifamycin  
               | • Bedaquiline–Pretomanid–Pyrazinamide  
               | • Levofloxacin Fluoroquinolone |
| III             | • Bedaquiline (TMC207) with OBR for MDR-TB Diarylquinoline  
               | • Delamanid (OPC-67683) with OBR for MDR-TB Nitro-dihydroimidazooxazole*  
               | • Pretomanid – Moxifloxacin – Pyrazinamide New chemical entity* |

* See “Resources” at the end of this course for a link to up-to-date TB drug trial information.

Source: TBFacts.org, 2016.
## Clinical Research Study Phases

<table>
<thead>
<tr>
<th>Phase</th>
<th>Patients</th>
<th>Length of Study</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20–100 healthy volunteers</td>
<td>Several months</td>
<td>Safety and dosage</td>
</tr>
<tr>
<td>II</td>
<td>Several hundred people with the disease</td>
<td>Several months–2 years</td>
<td>Efficacy and side effects</td>
</tr>
<tr>
<td>III</td>
<td>300–3,000 people with the disease</td>
<td>1–4 years</td>
<td>Efficacy and adverse reactions</td>
</tr>
<tr>
<td>IV</td>
<td>Several thousand people with the disease</td>
<td>Ongoing</td>
<td>Safety and efficacy</td>
</tr>
</tbody>
</table>

Source: FDA, 2016.

## Adherence Strategies

Nonadherence to TB treatment is a major problem in TB control. Poor compliance and frequent interruption to medication management may cause relapse, increased transmission, morbidity, the development of drug resistance, and higher costs to TB control. To facilitate patient adherence, involved healthcare providers establish and maintain programs that maximize patient access to care and train and supervise other healthcare providers to provide patient-centered care (CDC, 2013e).

Adherence strategies include patient education, case management, directly observed therapy (DOT), fixed-dose combination drugs, and self-administered therapy.

## Patient Education

When educating patients, topics include:

- What medication should be taken, how much, how often, and when
- Possible adverse reactions to the medications
- When to seek necessary medical attention
- Consequences of not taking medicine correctly
- TB infection control measures and potential need for isolation (CDC, 2013e)

Healthcare providers must take the time to clearly explain to patients when, how much, and how often the treatment medication needs to be taken, especially if the patient is not receiving DOT. Written instructions are also provided. Additionally, all patients with TB are advised to undergo voluntary counseling and testing for HIV infection.
CASE

Nikki, a female patient who is eight weeks pregnant, is diagnosed with latent TB infection. Based on Nikki’s teaching plan, the nurse midwife in the OB/GYN practice explains to Nikki:

- How her medication regimen works, including when, how much, and how often her medications should be taken
- That initiation of TB therapy should not be delayed for pregnancy alone, even during the first trimester
- That the Mantoux skin test is safe for pregnant women
- That infants whose breastfeeding mothers are taking isoniazid (INH) should receive supplemental pyridoxine
- That breastfeeding is not discouraged for women being treated with first-line antituberculosis drugs because the small concentrations of these drugs in breast milk do not produce toxic effects in the nursing infant

The nurse midwife reinforces patient teaching by providing Nikki with written instructions that she is encouraged to use at home and by highlighting the number she can call if she has any questions.

CASE MANAGEMENT

Case management is a possible strategy to ensure that patients complete their TB treatment. There are three elements of case management:

- Assignment of responsibility
- Systematic, regular review
- Planning to address any barriers to adherence

In case management, a health department employee (case manager, usually a nurse) is assigned primary responsibility for the management of specific patients. Case management is patient-centered. The case manager is held accountable for ensuring that his or her patients are educated about TB and its treatment, their therapy is continuous, and all patient contacts are examined. Some specific responsibilities may be assigned to other individuals (e.g., clinic supervisors, outreach workers, health educators, and social workers).

Whenever possible, a case manager with the same cultural and linguistic background as the patient is assigned to help tailor an individualized treatment plan and promote patient adherence to the plan.
A case manager is responsible for:

- Ensuring active TB patients get appropriate treatment
- Identifying patient contacts that potentially may be infected with TB
- Arranging for evaluation and treatment of patients with active or latent TB
- Conducting epidemiologic investigations of potential outbreaks
- Initiating prevention and control procedures
  (CDC, 2013e)

**DIRECTLY OBSERVED THERAPY**

DOT is the preferred case management strategy for all patients with TB. (See box above under “Treatment Regimens.”) In DOT, a designated healthcare worker watches a patient swallow every dose of the patient’s TB drugs and documents them. DOT can also be used for a patient with latent tuberculosis infection treatment if the resources are available. Incentives may be used to enhance adherence to therapy. They may be as simple as offering a cup of coffee and talking with a patient who is waiting in the clinic, or more complex, such as providing food and housing for a patient who is homeless (CDC, 2013e).

**FIXED-DOSE COMBINATION DRUGS**

The use of fixed-dose combination capsules or tablets may enhance patient adherence and reduce the risk of inappropriate monotherapy when treatment is self-administered or in DOT. Administration of fewer doses of TB drug therapy may promote compliance with the drug regime, since the process is simplified. Clinicians should become familiar with the management of TB using FDA-approved fixed-dose combination drugs (CDC, 2013e).

**SELF-ADMINISTERED THERAPY**

Patients are asked routinely about adherence at follow-up visits. Pill counts are routine, and urine and blood tests are used periodically to check for the presence of drug metabolites or blood serum levels.

Response to treatment is monitored closely. If the patient’s sputum culture remains positive after two months of drug treatment, the patient is reevaluated and DOT is considered for the remainder of treatment to ensure that the drugs are being taken.

Incentives and enablers may be used to enhance adherence to self-administered therapy and keeping clinic appointments. Some incentives may be money, food and drink, or articles of clothing. An enabler may be bus tickets for transportation to and from a clinic or doctor’s office (CDC, 2013e).
TB CONTROL PROGRAMS

Responsibility for successful TB treatment is assigned to the healthcare provider, not the patient. Healthcare providers who note that a particular TB patient has demonstrated the inability or unwillingness to adhere to a prescribed treatment regimen should consult the health department TB control program.

The TB control program has an administrative function and develops policies to assist healthcare personnel work with TB patients to promote their compliance. The TB control program is responsible for collecting epidemiological data, maintaining a registry of all TB patients, and reporting data to the Centers for Disease Control and Prevention (CDC) as well as the state TB control agency.

The TB control program then assists in evaluating the patient for causes of nonadherence and provides additional services, such as the provision of outreach workers, to enable the patient to complete the recommended therapy.

If these efforts are unsuccessful, the TB control program then takes appropriate action, such as seeking court-ordered DOT or, if all other measures fail, issuing the detention of a patient who is unwilling or unable to complete treatment, although he or she remains infectious, at risk of becoming infectious, or is at risk for drug-resistant TB (County of Los Angeles Public Health, 2016).

INFECTION PREVENTION

Effective TB infection prevention in healthcare settings depends on early detection, airborne infection isolation, and treatment of individuals with infectious TB. All healthcare settings need a TB infection-prevention program designed to detect TB disease early and to isolate and promptly refer or treat individuals who have TB. The specific operations of each TB infection-prevention program will differ depending on whether the program will provide healthcare or will triage and transfer patients with suspected or confirmed TB disease.

An effective TB infection-prevention program has three different levels of control:

1. **Administrative controls** help reduce the risk of exposure to individuals with potentially infectious TB.

2. **Environmental controls** help prevent the spread and reduce the concentration of infectious droplet nuclei.

3. **Individual respiratory protection** helps in situations that pose a relatively high risk for exposure to TB.

(CDC, 2016f)
Administrative Controls

The use of administrative controls is the primary strategy and the first level in the hierarchy for infection control. Administrative controls are measures intended primarily to reduce the risk of exposing uninfected individuals to those who have infectious TB. These controls include:

- Assigning responsibility for TB infection prevention within the healthcare setting
- Conducting a TB risk assessment
- Developing and implementing a written TB infection control plan
- Implementing effective work practices for the management of patients who may have TB
- Ensuring proper cleaning and sterilization/disinfection of potentially contaminated equipment
- Educating, training, and counseling healthcare workers about TB at the time of hire and annually
- Testing and evaluating healthcare workers who are at risk for TB or may be exposed to TB
- Coordinating efforts with the local health department
(CDC, 2016f)

Environmental Controls

The second level in the hierarchy is the use of environmental controls to prevent the spread and reduce the concentration of infectious droplet nuclei. Environmental controls include technologies for the removal or inactivation of *M. tuberculosis*. These technologies include:

- Controlling the source of infection by use of local exhaust ventilation
- Diluting and removing contaminated air by use of general ventilation
- Cleaning the air by use of high-efficiency particulate air (HEPA) filtration to filter nuclei droplets from the air
- Cleaning the air by ultraviolet germicidal irradiation (UVGI) through the use of special lamps that give off germicidal ultraviolet irradiation to destroy the tubercle bacilli
- Protecting the areas adjacent to the TB patient’s room by using an airborne infection isolation (AII) room
(CDC, 2013c; CDC, 2016f)
**USING AIRBORNE PRECAUTIONS**

All patients with confirmed drug-susceptible TB disease must remain under Airborne Precautions while hospitalized in an airborne infection isolation (AII) negative pressure room until they:

- Have three negative sputum smears collected on different days (one should be an early-morning specimen) collected in 8- to 24-hour intervals
- Demonstrate clinical improvement
- Are on anti-TB chemotherapy for at least 2 weeks

In patients with drug-resistant TB, infectiousness may last several weeks or even months. In these patients, the response to treatment is closely monitored and Airborne Precautions are maintained until infectiousness is ruled out by culture.

Continued precautions throughout hospitalization should be considered for patients with multidrug-resistant TB because these patients are more likely to experience treatment failure or relapse, which may prolong infectiousness.

Source: CDC, 2013e.

**Personal Respiratory Protection**

The third level in the infection control hierarchy is the use of personal respiratory protection in situations that pose a relatively high risk for exposure. The first two levels of the infection-control hierarchy (administrative and environmental controls) minimize the number of areas where exposure to infectious TB disease may occur. They also reduce, but do not eliminate, the risk in the few areas where exposures can still occur (CDC, 2013e).

Personal respiratory protection, as required by the Occupational Safety and Health Administration (OSHA), is recommended for use by individuals who are:

- Entering areas in which patients with suspected or confirmed infectious TB are being isolated
- Assisting during cough-inducing or aerosol-generating procedures performed on patients with suspected or confirmed infectious TB
- Working in other settings where administrative and environmental controls are not likely to protect them from inhaling infectious airborne droplet nuclei, such as jails, public health settings, or assistive-living facilities

Laboratory personnel conducting aerosol-producing procedures may also require respiratory protection; decisions concerning the use of personal respiratory protection in this setting should be made on a case-by-case basis. Aerosol-producing procedures are usually performed in
biological safety cabinets (BSC) with high-efficiency particulate air (HEPA) filters; however, if for some reason they are conducted outside of a BSC, laboratory personnel should wear a respirator (CDC, 2013e).

**CASE**

Esperanza is a 72-year-old woman who recently moved to California from Mexico. Her family takes her to the urgent care clinic because she is complaining of a persistent, productive cough lasting two months, fever, and lack of appetite. She has a prior history of TB treated in Mexico. A chest X-ray reveals pneumonia, and she is admitted to the hospital. Because she is considered high-risk for a recurrence of TB, she is admitted into an airborne infection isolation (AII) negative pressure room.

When her family comes to the hospital to visit, the nurse, Thomas, instructs them in Airborne Precautions to protect themselves from contracting TB. Thomas tells them that TB bacteria can spread in droplets from the patient, usually when she coughs. The droplets then remain airborne for a few minutes until they land on the surfaces in the room. The family is shown where to find masks, gowns, and gloves to don before entering Esperanza’s room. They are told the room is specially pressurized and that the air in the room is filtered.

**PERSONAL RESPIRATORY PROTECTION PROGRAM**

OSHA requires healthcare settings that use respiratory protection to prevent the inhalation of infectious droplet nuclei to develop, implement, and maintain a personal respiratory protection program. All healthcare workers who use respiratory protection must be included in the program. The two most critical elements of a personal respiratory protection program are the training of healthcare workers and the selection of appropriate, well-fitting respirators.

**Annual Training**

Healthcare workers must participate in annual training that includes:

- Nature, extent, and hazards of TB disease in the healthcare setting
- Risk assessment and its relationship to the respirator program
- Signs and symbols used to show that respirators are required in an area
- Reasons for using respirators
- Environmental controls
- Reasons for selecting a particular respirator for a given hazard
- Operation, capabilities, and limitations of respirators
- Cautions about facial hair (since beards and bushy mustaches may interfere with maintaining a tight seal of a mask around the face)
• Review of OSHA regulations
• Opportunity to handle and wear a respirator until proficient
• Compilation of printed lecture materials for later use as a reference
• Instructions to refer all respirator problems immediately to the respirator program administrator (OSHA, 2013)

**Fitting Respiratory Protection Devices**

Healthcare workers are required to wear respirator masks to protect themselves from airborne infections. To be effective, the respirator masks must fit the wearer extremely well. Fit testing must be performed by a trained examiner to ensure the mask fits each person properly. Retesting is performed annually to ensure ongoing proper fit. Any facial hair must be shaved off to ensure the respirator mask fits properly. During fit testing, the wearer is encased in a plastic hood while wearing the mask. An aerosol-delivered scent is squirted into the hood to determine if the wearer is able to smell it, which indicates an improper fit (CDC, 2013g).

Healthcare worker wearing a respirator. (Source: CDC, 2013e.)

Infectious TB patient wearing a surgical mask (Source: CDC, 2013e.)
INFECTIOUS PATIENTS

In general, patients who have suspected or confirmed TB disease are considered infectious if they:

- Have disease in the lungs, airway, or larynx, or
- Are coughing, or
- Are undergoing cough inducing procedures, or
- Have positive AFB sputum smears, and
  - Are not on anti-tuberculosis chemotherapy, or
  - Have just started chemotherapy, or
  - Have a poor clinical or bacteriologic response to chemotherapy

Source: CDC, 2013e.

CASE

Kim Myong Cha is admitted to a medical center for definitive treatment of a solitary XDR TB lung lesion that has proven refractory to chemotherapy. She is scheduled for a thoracotomy to remove the lesion.

Her nursing team on the inpatient unit is comfortable caring for her, but the OR/PACU transporters, staff in the preoperative holding area, and some of the OR and PACU personnel have expressed concern about possible exposure. Before long, the rumor mill is in full cry, with misinformation outweighing evidence-based statements.

Two days before the surgery date, the OR manager and the chief of anesthesia schedule a meeting with the OR and anesthesia personnel assigned to the case, two senior OR/PACU transporters, the thoracic surgical team, and the PACU and ICU managers. They practice a virtual tracer methodology exercise using a flow chart to follow the patient from the moment she moves to the transport gurney in her room until she is transferred back to her bed on the nursing unit after her stays in PACU and the surgical ICU.

By doing so, they identify precautions specific to her safe and compassionate care, to include:

1. Providing instruction on appropriate PPE (personal protective equipment) for the patient and all staff who will be directly interacting with her
2. Having only the patient and two transport personnel on the elevator that will bring her from the 7th to the 4th floor
3. Timing transport from the nursing unit so that she will be moved directly to the OR, bypassing the holding area
4. Providing appropriate TB screening prior to the case for any of the patient’s assigned team members who request it

5. Providing appropriate TB screening after the case for any of the patient’s assigned team members who request it

The patient-specific variations are discussed at shift reports so that all the OR, PACU, and anesthesia personnel are aware of the evidence-based precautions to be practiced on the day of surgery. Staff are strongly encouraged to avoid speculation and to bring any further questions or concerns to their supervisors so that facts may be used to counter rumors.

Community Tuberculosis Control

State and local health departments have the primary responsibility for preventing and controlling TB. However, those who provide TB services in settings such as private clinics, managed care organizations, HIV clinics, homeless shelters, long-term care facilities, emergency medical services, correctional facilities, and hospitals also have responsibility for preventing and controlling TB in their communities (CDC, 2013e).

PRIORITY STRATEGIES

Prevention and control is conducted through the coordination of healthcare providers in a variety of settings to ensure the provision of direct services for TB patients. Prevention and control includes three vital strategies:

1. Identifying and treating all individuals who have TB disease (this means seeking out and diagnosing cases of TB and ensuring that patients complete appropriate therapy)

2. Finding and evaluating individuals who have been in contact with TB patients to determine whether they have acquired a TB infection or disease, then treating them accordingly

3. Testing high-risk groups for TB infection to identify candidates for treatment of latent infection and to ensure the completion of treatment
   (Cecilio et al., 2015)

LOCAL HEALTH DEPARTMENT ROLE

The local health department achieves the three critical strategies described above by working in cooperation with healthcare providers offering direct services to TB patients. It is crucial to coordinate care with other healthcare providers and facilities in the following areas:

- Overall planning and policy development
- Identification of individuals who have clinically active TB
• Maintaining a registry of all TB patients
• Management of individuals who have disease or who are suspected of having disease
• Finding and evaluating those who have been in contact with individuals infected with *M. tuberculosis*
• Identification and management of individuals infected with *M. tuberculosis*
• Laboratory and diagnostic services
• Data collection and analysis, including reporting to the CDC
• Legal authority to detain TB patients for examination, isolation, or treatment to protect the public’s health
• Training and education
  (County of Los Angeles Public Health, 2016)

In the United States, it is the responsibility of the public health department to identify, interview, and test the contacts of people positive for TB. The CDC recommends that a TB-positive patient be interviewed within one day of laboratory results being reported to the health department. Public health nurses should visit possible exposure sites within three days of the interview, with possible contacts tested within three working days after that. Without treatment, about 5% to 10% of infected persons will develop TB disease (CDC, 2014b).

**TB REPORTING REQUIREMENTS**

Early detection of tuberculosis is essential to ensure initiation of appropriate treatment and to identify contacts that may also be infected with TB. The CDC recommends clinicians report positive cases of TB to the nearest health department within two days of identification. Laboratories should report positive test results to the healthcare provider who ordered the test within one day. However, reporting requirements are specific to the county or municipality in which the local health department is located (County of Los Angeles Public Health, 2016b).

Public health departments throughout the United States and its territories maintain TB control programs. One example, described below, is the state of Indiana. (See “Resources” at the end of this course for a link to a list of state TB control programs.)

**INDIANA TB CONTROL PROGRAM**

In Indiana the Department of Health maintains a state TB control program with the help of a 10- to 15-member physician medical advisory board (MAB). The TB control program plans for the reduction and elimination of TB in the state through surveillance, developing policies, assisting local health departments and healthcare providers, providing case management oversight, and raising public awareness.
To achieve these goals the Indiana State Department of Health:

- Maintains, analyzes, and reports surveillance data on TB in Indiana
- Consults with local health departments about the diagnosis, treatment, management, and investigation of TB cases
- Monitors and evaluates local TB programs
- Provides programs to local health departments
- Provides TB medications
- Provides education to community organizations and healthcare personnel
- Refers immigrants who enter Indiana with TB to local health departments

Indiana state guidelines include skin testing, treatment, and sputum collection.

Guidelines call for **skin test screening** for the following groups:

- Close contacts of TB patients
- HIV-positive patients
- Those with a history of inadequately or incomplete TB treatment
- IV drug users
- Residents and employers of crowded facilities
- Healthcare workers serving high-risk populations
- People born outside of the United States and Canada
- Medically underserved, low-income population
- Infants, children, and adolescents exposed to adults in high-risk categories
- Locally defined high-prevalence groups (e.g., homeless, migrant workers)

Recommended **guidelines for treating latent TB infection** (LTBI) include:

- Isoniazid (INH) for 9 months
- Rifampin for 4 months for adults and 6 months for children
- Dosing the same as for active TB cases

Patients with the following conditions are not candidates for the alternative, short treatment regimens:

- Hepatitis
- End-stage liver disease
Every documented or suspected case of TB must be reported to the health department within 72 hours.


**BCG VACCINATION**

The bacillus Calmette-Guérin (BCG) vaccine is a live vaccine derived from a strain of *M. bovis* that was attenuated by Calmette and Guérin at the Pasteur Institute in Lille, France. An early version of BCG was first administered to humans in 1921. Since that time, many different strains have been derived and are used today throughout the world. The BCG vaccination is not generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable effectiveness of the BCG vaccine against pulmonary TB, and the vaccine’s interference with the ability to determine tuberculin reactivity.

Use of the BCG vaccination as a TB prevention strategy in the United States and most low-incidence countries is limited because its effectiveness in preventing infectious forms of TB is uncertain. The BCG vaccine should be considered only for selected individuals who meet specific criteria, such as neonatal BCG vaccination against miliary and meningeal tuberculosis in infancy and childhood. The use of the BCG vaccine should be undertaken only after consultation with local health authorities and experts in the management of TB.

The BCG vaccination may cause a positive reaction to the tuberculin skin test. Thus, it may complicate decisions about prescribing treatment for LTBI for BCG-vaccinated individuals who have a positive skin-test result (Sotgiu & Migliori, 2016).

**BCG Vaccination for an Infant or Child**

BCG vaccine continues to be administered in infants at birth in 150 countries where tuberculosis is endemic (Sotgiu & Migliori, 2016; Zumla, 2013). However, in the United States, BCG vaccination should only be considered for an infant or child who has a negative tuberculin skin-test result in either of the following circumstances:

- The child is exposed continually to an untreated or ineffectively treated patient who has infectious pulmonary TB and the child cannot be separated from the infectious patient or given long-term primary treatment for infection
• The child is exposed continually to a patient who has infectious pulmonary TB caused by *M. tuberculosis* strains resistant to isoniazid (INH) and rifampin (Rifadin) and the child cannot be separated from the infectious patient (CDC, 2013e)

**BCG Vaccination for Healthcare Workers**

The BCG vaccination of healthcare workers is considered on an individual basis in settings in which:

• A high percentage of TB patients are infected with MDR-TB
• Transmission of such drug-resistant *M. tuberculosis* strains to healthcare workers and subsequent infection are likely
• Comprehensive TB infection-control precautions have been implemented without successful outcome (CDC, 2013e)

**Contraindications for BCG Vaccination**

The BCG vaccine is contraindicated in individuals who have an impaired immune response from the following:

• HIV infection
• Congenital immunodeficiency
• Leukemia
• Lymphoma
• Generalized malignancy
• High-dose steroid therapy
• Alkylating agents
• Antimetabolites
• Radiation therapy (CDC, 2013e)

BCG vaccination is not administered during pregnancy. Even though no harmful effects of BCG vaccination on the fetus have been observed, further studies are needed to prove its safety (CDC, 2013e).
Tuberculin Reactions in BCG-Vaccinated Individuals

Many highly endemic countries still appropriately vaccinate infants with BCG as part of their TB control programs. In individuals vaccinated with BCG, sensitivity to tuberculin is highly variable, depending upon the strain of BCG used and the group vaccinated.

TST results are used to support or exclude a diagnosis of LTBI. The TST in individuals vaccinated with BCG should be interpreted using the same criteria as for those not BCG-vaccinated. The booster phenomenon may occur among individuals who have had a prior BCG vaccination (CDC, 2013e).

Other TB Vaccines

Through a major international effort, a range of vaccines are being studied both as primary immunogens to replace BCG and as boosters for BCG. Most new vaccines are a recombinant version of the current BCG vaccine and are still in animal trials (Henao-Tamayo et al., 2015).

TB AND HIV

Management of HIV-related TB disease is complex, and the clinical and public health consequences associated with the failure of treatment are serious. Care for HIV-related TB is provided by, or in consultation with, experts in the management of both TB and HIV disease. The choice of drugs, timing of treatment, and other factors may vary for HIV-positive individuals. This is especially challenging in the care of pulmonary TB in children and adolescents with HIV infection, for whom the optimal treatment is unknown (CDC, 2013e).

HIV Testing for Suspected TB Patients

The WHO (2016c) recommends HIV testing for all patients who present with signs or symptoms of tuberculosis, whether it is suspected or already confirmed. The chances for developing TB are 26 to 31 times greater for persons that are HIV positive.

TB is often the first clinical indication that a person has an HIV infection. TB services can be an extremely important entry point to HIV prevention, care, and treatment. The HIV status of TB patients makes a difference to their TB treatment. Detecting HIV infection in a TB patient is also critical for the TB patient’s household members. HIV-positive TB patients may have household members who are also living with HIV.

A person with both TB disease and an HIV infection has an AIDS-defining condition, since the TB in this instance is an opportunistic infection. Clinicians who are supervising the TB care of HIV-positive individuals should consult with the appropriate medical staff so that they can teach the client accurately and provide appropriate supervision of care. Untreated latent TB infection can quickly become active TB for people with HIV due to the weakness of their immune system (CDC, 2013e).
Mortality Rates in TB/HIV Comorbidity

Tuberculosis leads to an increase in HIV proliferation and accelerates progression of HIV infection, resulting in high mortality rates. Early initiation of antiretroviral therapy results in a reduction in mortality. Patients with tuberculosis who do not receive antiretroviral therapy with very low numbers of CD4+ cells have a high risk of death (Zumla et al., 2013).

Worldwide, TB is one of the leading causes of death for people who are also HIV positive. As an opportunistic infection, persons with TB and HIV exhibit shorter lifespans when the TB is untreated (CDC, 2013c).

CONCLUSION

There has been a drastic reduction in the number of TB cases in the United States, with TB now affecting primarily the elderly and immunocompromised. In the rest of the world, TB is much more prevalent, with the World Health Organization estimating that approximately one third of the world population is positive for the TB bacteria. In 2016 the WHO announced an “End TB Strategy,” with plans to eliminate TB globally by 2030.

In the United States, local public health departments carry the responsibility for taking reports of suspected and verified cases of TB from healthcare personnel and laboratories. The health departments then evaluate patient environments and contacts to identify other possible sources of infection. Creating treatment regimes, monitoring drug susceptibility and treatment outcomes, conducting directly observed therapy (DOT), and promoting community education are also in the purview of local health departments.

In the hospital setting, institutions carry administrative responsibility to identify, treat, and prevent the transmission of TB. Diagnosis of TB is usually made by a review of the symptoms (persistent cough, hemoptysis, appetite loss, weight loss, and fever); history, including risk factors; and skin, sputum, or blood testing. The two most common forms of testing in the United States are the Mantoux tuberculin skin test (TST) and the Quantiferon-TB Gold blood test (QTB-G). Other tests, such as sputum culture for acid-fast bacillus (AFB) and chest radiography, are used but not considered as definitive.

Treatment of TB consists of a combination of drugs, such as isoniazid and rifampin, usually for six to nine months. Recent research indicates that a much lower number of doses (12) over a period of three months is available but not effective for all patients. Some patients must be observed taking their medications to ensure compliance in a DOT regime.

Multiple drug-resistant TB has become more prevalent, causing changes to be needed in the conventional treatment of TB. Bedaquiline and Delamanid are two new anti-TB drugs that have been conditionally approved by the FDA for use in TB patients, particularly those whose infection is not sensitive to the first-line, traditionally effective TB drugs.
In the healthcare setting, transmission of the bacteria is prevented by the use of a specially designed patient room and personal protective equipment. An airborne infection isolation (AII) room contains negative pressure that prevents the air from leaving the room where it is filtered via a high-efficiency particulate air (HEPA) filter to prevent adjacent areas from becoming contaminated. Hospital personnel and visitors are required to wear gloves, gowns, and masks when in contact with the patient. Particulate respirator masks are required for healthcare personnel caring for a TB positive patient that require annual fit testing to ensure efficacy. The patient must be masked when transported within the hospital for procedures.

Recent work has been done to develop new vaccines for TB. The bacillus Calmette-Guérin (BCG) vaccine has been used since 1921 to prevent the spread of TB. This is not commonly used in countries such as the United States, where there is a low incidence of TB. Many of the new vaccines are recombinant versions of BCG, but they are in the animal trial stages.

RESOURCES

Find TB Resources (CDC)
http://findtbrsources.cdc.gov

Global Tuberculosis Institute (New Jersey Medical School)
http://web.njms.rutgers.edu/ntbcweb/

National Tuberculosis Controllers Association
http://www.tbcontrollers.org

State TB control offices (CDC)
http://www.cdc.gov/tb/links/tboffices.htm

Stop TB Partnership
http://stoptb.org

TB Alliance
http://www.tballiance.org

TB drugs
http://www.tbfacts.org/tb-drugs/#thash.tywQuRGC.dpuf

TB Regional Training and Medical Consultation Centers (RTMCCs)
http://www.cdc.gov/tb/education/rtmc/

TB treatment guidelines (CDC)
http://www.cdc.gov/tb/publications/guidelines/Treatment.htm

Tuberculosis (American Lung Association)
http://lung.org/lung-disease/tuberculosis/

Tuberculosis (World Health Organization)
http://who.int/tb/en/
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Sotgiu G & Migliori GB. (2016). Long-term protectiveness of BCG. *The Lancet Infectious Diseases*, 16(2), 140–2. doi:http://dx.doi.org/10.1016/S1473-3099(15)00414-4


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1. Tuberculosis is most commonly spread from someone with the disease via:
   a. Poor handwashing.
   b. Coughing, sneezing, and talking.
   c. Transfusion of red blood cells and other blood products.
   d. Normal respiration.

2. Which was the first antibiotic developed to treat tuberculosis but is no longer a first-line TB medication?
   a. Quinine
   b. Isoniazid (INH)
   c. Penicillin (Bicillin)
   d. Streptomycin

3. A significant reason that TB cases increased in the 1980s and are still occurring in the United States is due to:
   a. Limited access to medications.
   b. Immunosuppression caused by HIV.
   c. Poor medical management of the disease.
   d. An increase in concurrent respiratory infections.

4. Depending on the environment, droplet nuclei containing tubercle bacilli can remain suspended in the air for:
   a. A few seconds.
   b. Up to 30 seconds.
   c. A few minutes.
   d. Prolonged periods of time.

5. Drug-resistant TB is different from drug-susceptible TB in that it:
   a. Is transmitted differently.
   b. Is more infectious.
   c. Can result in prolonged periods of infectiousness.
   d. Can produce droplets that are more potent.
6. Tuberculosis found in places in the body such as the brain or bones is referred to as:
   b. Mycobacterium.
   c. Extrapulmonary.
   d. Pan-tuberculosis.

7. In the hospital, transmission of TB is best prevented by placing the infectious patient:
   a. Under Airborne Precautions.
   b. With head elevated, wearing a particulate respirator mask.
   c. At the end of a hall in a single-patient room.
   d. In a directly observed therapy (DOT) program.

8. Which is a correct statement about a patient with latent TB infection but no TB disease?
   a. The patient requires medication to prevent TB disease.
   b. Public health authorities consider this patient to represent a TB case.
   c. Others may become infected with TB bacteria through contact with this patient.
   d. The patient will likely display symptoms of chills and fever.

9. Which is not a common symptom of pulmonary TB?
   a. Fever
   b. Fatigue
   c. Hemoptysis
   d. Nausea

10. When obtaining a health history, the nurse asks the patient suspected of having TB about his or her:
    a. History of asthma.
    b. HIV status.
    c. Household members’ names.
    d. Dietary habits.

11. Individuals who should be tested for TB infection due to a higher risk for TB exposure include:
    a. Smokers.
    b. Injection drug users.
    c. Restaurant workers.
    d. Sexually active young adults.
12. Among patients who test positive for tuberculosis infection, which is at **highest** risk for showing symptoms of TB disease?
   a. A patient who is of Asian/Pacific Islander heritage
   b. An older adult patient who is a recovering alcoholic
   c. A patient with LTBI who stops treatment
   d. A female patient with type 1 diabetes

13. Which is a **correct** statement regarding the Mantoux tuberculin skin test?
   a. Reaction to the test should be read within 48 to 72 hours after injection.
   b. Severe swelling and redness is normal in the injection area.
   c. Certain foods can cause a false positive response.
   d. It is recommended that the test be repeated every six months.

14. Accurate interpretation of results from the Mantoux tuberculin skin test depends on the size of the induration and the:
   a. Severity of pain at the injection site.
   b. Time since the patient’s exposure.
   c. Patient’s risk factors.
   d. Agency’s supplemental instructions.

15. An advantage to using the QFT-G test for the diagnosis of tuberculosis is that:
   a. It is not subject to reader bias.
   b. The results are available immediately.
   c. Only two visits to draw blood are required.
   d. It is less expensive than formerly used tests.

16. Which is a **correct** statement regarding a TB skin test (TST) for a pregnant patient?
   a. A TST is not needed unless the patient starts showing symptoms.
   b. A TST is safe and reliable throughout the course of pregnancy.
   c. Women are advised to avoid a TST in the first trimester of their pregnancy.
   d. False-positive TST results are sometimes caused by pregnancy hormones.

17. Which condition increases the risk that a latent TB infection will progress to active TB disease?
   a. Pregnancy
   b. Trauma
   c. Obesity
   d. Crohn’s disease
18. Which is a correct statement regarding the mechanism of LTBI treatment?
   a. Only one LTBI regimen has proven successful in all populations.
   b. Close contacts of someone with LTBI will test positive for tuberculosis.
   c. Treatment of LTBI is essential to the control and elimination of TB disease.
   d. Young children do not require different LTBI treatment from that of adults.

19. The advantage of a six-month dosing regimen for TB medications is that it:
   a. Works equally well for both active and latent TB infections.
   b. Only requires once-a-week dosing.
   c. Is more cost-effective, thereby encouraging compliance.
   d. Does not require follow-up testing.

20. The duration of therapy for pulmonary TB depends on the drug selection, the drug susceptibility test results, and the:
   a. Patient’s response to therapy.
   b. Family’s support.
   c. Patient’s weight at time of diagnosis.
   d. Patient’s age.

21. Which is the best example of directly observed therapy (DOT)?
   a. A family member watches a healthcare worker give a patient a bottle of prescribed pills.
   b. A physician sees the patient once a month and counts the remaining pills in the medication bottles.
   c. A healthcare worker watches the patient swallow each dose of the prescribed drugs.
   d. The nurse uses a urine test to measure the presence of medicine in the patient’s urine.

22. Which healthcare agency will collaborate with primary care providers to develop and monitor a treatment plan for those patients with latent or active TB?
   a. Centers for Disease Control and Prevention (CDC)
   b. Local health department
   c. Joint Commission
   d. U.S. Department of Health and Human Services
23. During testing to fit N95 particulate respirator masks, healthcare personnel are instructed to:
   a. Shave off any facial hair.
   b. Refit or adjust the mask once every three years.
   c. Use surgical masks if N95 masks are uncomfortable.
   d. Place the N95 mask on the patient.

24. A patient with TB is considered infectious until he or she:
   a. Has completed a 3-month anti-tuberculosis chemotherapy drug regimen.
   b. Starts a medication regime.
   c. Demonstrates clinical improvement with cessation of symptoms.
   d. Stops coughing, regardless of completing a medication regime.

25. Which statement about BCG vaccination is not true?
   a. BCG vaccination is used for most HIV patients.
   b. BCG vaccination may cause a positive reaction to the tuberculin skin test.
   c. BCG vaccination is contraindicated in pregnant women.
   d. BCG vaccination is used for infants at birth in most regions where tuberculosis is endemic.

26. Which is a true statement in regard to patients with tuberculosis and HIV?
   a. Most HIV and TB drugs are compatible.
   b. The mortality rate for those with HIV and TB is the same as TB alone.
   c. The TB medication treatment regime is the same for patients with or without HIV.
   d. TB is often the first clinical indication that a person has an HIV infection.