

DRUG THERAPY IN TUBERCULOSIS

Debjit Bhowmik, Chiranjib , R.Margret Chandira*, B.Jayakar, K.P.Sampath Kumar

Rajiv Gandhi College of Pharmacy, Uttar Pradesh
Vinayaka missions college of Pharmacy, Salem
Coimbatore medical college, Coimbatore, Tamilnadu
Email-margretchandira@yahoo.com

ABSTRACT

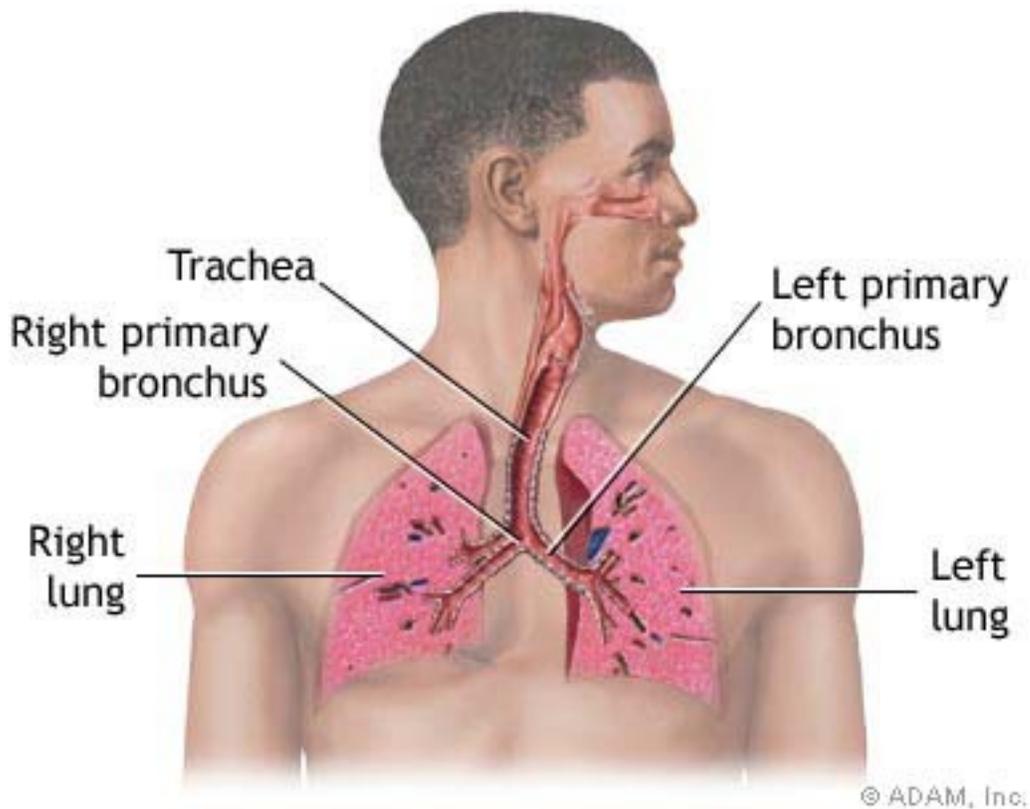
Tuberculosis is a chronic infection caused by the bacteria *Mycobacterium tuberculosis* (and occasionally other variants of Mycobacterium). It usually involves the lungs, but other organs of the body can also be involved. Tuberculosis (TB) is a disease caused by bacteria called Mycobacterium tuberculosis. The bacteria usually attack the lungs. But, TB bacteria can attack any part of the body such as the kidney, spine, and brain. If not treated properly, TB disease can be fatal. TB is spread through the air from one person to another. The bacteria are put into the air when a person with active TB disease of the lungs or throat coughs or sneezes. People nearby may breathe in these bacteria and become infected. However, not everyone infected with TB bacteria becomes sick. People who are not sick have what is called latent TB infection. People who have latent TB infection do not feel sick, do not have any symptoms, and cannot spread TB to others. But, some people with latent TB infection go on to get TB disease. People with active TB disease can be treated and cured if they seek medical help. Even better, people with latent TB infection can take medicine so that they will not develop active TB disease. It's important to take the medicine for active TB for at least 6 months. Almost all people are cured if they take their medicine. If tests still show an active TB infection after 6 months, then treatment continues for another 2 or 3 months. Most people with latent TB are treated with only one antibiotic that they take for 9 months. This reduces their risk for getting active TB. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the US population test positive. It is estimated that the US has 25,000 new cases of tuberculosis each year, 40% of which occur in immigrants from countries where tuberculosis is endemic. The World Health Organization (W.H.O.) declared TB a global health emergency in 1993, and the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between 2006 and 2015. Since humans are the only host of Mycobacterium tuberculosis, eradication would be possible: a goal that would be helped greatly by an effective vaccine. Standard therapy for pulmonary TB includes isoniazid and rifampin for 6 months along with pyrazinamide for the first 2 months (isoniazid and rifampin without pyrazinamide may be used for 9 months, if necessary). Treatment consists of three drugs that are effective against the organism.

INTRODUCTION

Tuberculosis (TB) is an infection caused by slow-growing bacteria that grow best in areas of the body that have lots of blood and oxygen. That's why it is most often found in the lungs. This is called pulmonary TB. But TB can also spread to other parts of the body, which is called extrapulmonary TB. Treatment is often a success, but it is a long process. It takes about 6 to 9 months to treat TB. In 1993, the World Health Organization (WHO) declared tuberculosis a global emergency. According to the WHO, worldwide incidence of tuberculosis (TB) may have peaked in 2005. Tuberculosis infection is responsible for more deaths than any other infectious disease. Once called consumption, TB is a highly contagious, persistent disease characterized by the formation of hard grayish nodules, or tubercles. The disease is most often caused by the bacterium *Mycobacterium tuberculosis* and usually occurs in the lungs (the initial site of infection), but it also can occur in other organs. Between two to eight weeks after being infected with *M. tuberculosis*, a person's immune system responds to the tuberculosis germ by walling off infected cells. From then on the body maintains a standoff with the infection, sometimes for years. Most people undergo complete healing of their initial infection, and the bacteria eventually die off. A positive tuberculosis skin test, and old scars on a chest x-ray, may provide the only evidence of the infection. If, however, the body's resistance is low because of aging, infections such as HIV, malnutrition, or other reasons, the bacteria may break out of hiding and cause active tuberculosis. Because its signs and symptoms are easily confused with those of many other (usually respiratory) diseases, tuberculosis can be difficult to diagnose. Common symptoms are cough that is worse in the morning and may include hemoptysis (i.e., blood in the sputum), chest pain, night sweats, and breathlessness (dyspnea). Ninety percent of those infected with *M. tuberculosis* mount an effective immune response and never develop the disease. The reason for treating a patient with asymptomatic tuberculosis infection is that there is a 5% risk for developing TB during the first year after infection and an additional 5% risk for developing TB over a lifetime. Also, treatment of asymptomatic TB infection is much simpler than treating tuberculosis. Treatment lasts 6 months in an adult without HIV, 12 months in an adult with HIV, and 9 months in children. This drug has side effects. This is the second most commonly used drug. Generally, the course of therapy with rifampin is 6 to 12 months. If a patient has been exposed to multidrug-resistant *Mycobacterium tuberculosis*, individualization of drug therapy is required. Side effects have been noted with this drug. With appropriate antibiotic treatment, tuberculosis can be cured in more than nine out of ten patients. Successful tuberculosis treatment depends on close cooperation between the patient and doctor and other health care workers. Tuberculosis treatment usually combines several different antibiotic drugs which are given for at least six months, sometimes for as long as 12 months. Patients must take their medicine on time every day for the 6 to 12 months. Some tuberculosis patients stop taking their prescribed medicines because they may feel better after only a couple of weeks of treatment. Another reason they may stop taking their medicine is because tuberculosis drugs can have unpleasant side effects.

TUBERCULOSIS CAUSES

All cases of TB are passed from person to person via droplets. When someone with TB infection coughs, sneezes, or talks, tiny droplets of saliva or mucus are expelled into the air, which can be inhaled by another person. Once infectious particles reach the alveoli (small saclike structures in the air spaces in the lungs), another cell, called the macrophage, engulfs the TB bacteria. Then the bacteria are transmitted to the lymphatic system and bloodstream and spread to other organs occurs. The bacteria further multiply in organs that have high oxygen pressures, such as the upper lobes of the lungs, the kidneys, bone marrow, and meninges -- the membrane-like coverings of the brain and spinal cord. When the bacteria cause clinically detectable disease, you have TB. People who have inhaled the TB bacteria, but in whom the disease is controlled, are referred to as infected. Their immune system has walled off the organism in an inflammatory focus known as a granuloma. They have no symptoms, frequently have a positive skin test for TB, yet cannot transmit the disease to others. This is referred to as latent tuberculosis infection or LTBI.



- **Figure-Pulmonary Tuberculosis in lung**
-
-
- **RISK FACTORS**
- Risk factors for TB include the following:

- ❖ HIV infection
- ❖ low socioeconomic status
- ❖ alcoholism
- ❖ homelessness
- ❖ crowded living conditions
- ❖ diseases that weaken the immune system
- ❖ migration from a country with a high number of cases
- ❖ health-care workers

TUBERCULOSIS SYMPTOMS

Even then the symptoms -- loss of weight, loss of energy, poor appetite, fever, a productive cough, and night sweats -- might easily be blamed on another disease. Only about 10% of people infected with *M. tuberculosis* ever develop tuberculosis disease. Many of those who suffer TB do so in the first few years following infection, but the bacillus may lie dormant in the body for decades. Although most initial infections have no symptoms and people overcome them, they may develop fever, dry cough, and abnormalities that may be seen on a chest X-ray. This is called primary pulmonary tuberculosis. Pulmonary tuberculosis frequently goes away by itself, but in 50%-60% of cases, the disease can return. Tuberculous pleuritis may occur in 10% of people who have the lung disease from tuberculosis. The pleural disease occurs from the rupture of a diseased area into the pleural space, the space between the lung and the lining of the abdominal cavity. These people have a nonproductive cough, chest pain, and fever. The disease may go away and then come back at a later date. In a minority of people with weakened immune systems, TB bacteria may spread through their blood to various parts of the body. This is called miliary tuberculosis and produces fever, weakness, loss of appetite, and weight loss. Cough and difficulty breathing are less common. Generally, return of dormant tuberculosis infection occurs in the upper lungs. Symptoms include common cough with a progressive increase in production of mucus and coughing up blood. Other symptoms include the following: fever, loss of appetite, weight loss, and night sweats. About 15% of people may develop tuberculosis in an organ other than their lungs. About 25% of these people usually had known TB with inadequate treatment. The most common sites include the following: lymph nodes, genitourinary tract, bone and joint sites, meninges, and the lining covering the outside of the gastrointestinal tract.

PREVENTION

Treatment to prevent TB in a single person aims to kill walled-up germs that are doing no damage right now but could break out years from now and become active. If you should be treated to prevent sickness, your doctor usually prescribes a daily dose of isoniazid (also called INH), an inexpensive TB medicine. You will take INH for up to a year, with periodic checkups to make sure you are taking it as prescribed and that it is not causing undesirable side effects. Treatment also can stop the spread of TB in large populations. The tuberculosis vaccine, known as bacille Calmette-Guérin (BCG) may prevent the spread of tuberculosis and tuberculous meningitis in children, but the vaccine does not necessarily protect against pulmonary tuberculosis. It can, however, result in a false-positive tuberculin skin test that in many cases can be differentiated by the use of the QuantiFERON-TB Gold test mentioned above. Health officials generally recommend the vaccine in countries or communities where the rate of new infection is greater than 1% per year. BCG is not generally recommended for use in the United States because there is a very low risk of tuberculosis infection. It may be considered for very select patients at high risk for tuberculosis and who meet special criteria. TB is spread through the air from one person to another. The bacteria are put into the air when a person with active TB disease of the lungs or throat coughs or sneezes. People nearby may breathe in these bacteria and become infected. When a person breathes in TB bacteria, the bacteria can settle in the lungs and begin to grow. From there, they can move through the blood to other parts of the body, such as the kidney, spine, and brain. TB in the lungs or throat can be infectious. This means that the bacteria can be spread to other people. TB in other parts of the body, such as the kidney or spine, is usually not infectious. People with active TB disease are most likely to spread it to people they spend time with every day. This includes family members, friends, and coworkers.

EXAMS AND TESTS

Diagnosing active TB in the lungs

Doctors diagnose active tuberculosis (TB) in the lungs (pulmonary TB) by using a medical history and physical examination, and by checking your symptoms (such as an ongoing cough, fatigue, fever, or night sweats). Doctors will also look at the results of: Sputum cultures. Testing mucus from the lungs (sputum culture) is the best way to diagnose active TB. If TB bacteria grows from your samples, sensitivity testing is done on the bacteria. These tests will show which medications will kill the bacteria. Results of sensitivity tests can take between 1 and 6 weeks because TB-causing bacteria grow very slowly. Your doctor may start treatment before results are returned if it's likely that you have TB. Researchers are working on new tests that may give quicker results. Chest. A chest X-ray cannot diagnose active TB. A chest X-ray usually is done if you have: A positive tuberculin skin test (also called a TB skin test, PPD test, or Mantoux test). Symptoms of active TB,

such as a persistent cough, fatigue, fever, or night sweats. An uncertain reaction to the tuberculin skin test because of a weakened immune system, or to a previous bacille Calmette-Guerin (BCG) vaccination.

Diagnosing latent TB in the lungs

A tuberculin skin test will show whether you have latent TB. The test also will show if you have ever had a TB infection. See an illustration of a tuberculin skin test. QuantiFERON-TB Gold is a blood test that has been approved by the U.S. Food and Drug Administration (FDA) to help detect latent TB. It can help diagnose TB when results from a tuberculin skin test are uncertain. The test can also tell if a person who has had a BCG vaccination has a TB infection. It requires only one visit to the doctor or clinic, instead of two visits as required for the tuberculin skin test.

INCIDENCE AND PREVALENCE

Mycobacterial disease is one of the world's most difficult health problems. One-third of the population worldwide is infected with TB. Of these, 8 to 10 million develop active disease and according to the World Health Organization (WHO), 2 million die each year. It is the greatest cause of death in women of reproductive age; 900 million women are currently infected. Of these, 2.5 million will develop active disease and 1 million will die. According to WHO, every year more than 1.5 million TB cases occur in sub-Saharan Africa; nearly 3 million cases occur in Southeast Asia; and over 250,000 occur in Eastern Europe. AIDS (autoimmune deficiency syndrome) with coexistent mycobacterium infection is bringing TB back into Western cities and seriously threatens health services in the developing world. The rate of tuberculosis infection in the United States had been declining steadily until 1984 and then increased. Numerous factors account for the resurgence of tuberculosis in the United States and in Europe. They include the following:

- ❖ Emergence of multidrug-resistant strains of *M. tuberculosis*
- ❖ Erosion of systems for diagnosis and treatment of the disease
- ❖ Immigration of infected persons from countries where TB is prevalent
- ❖ Prevalence of HIV (human immunodeficiency virus) infection and AIDS
- ❖ Reactivation of disease in the elderly
- ❖ Socioeconomic decline in urban areas

The rapid response of state and federal agencies in the United States has averted a potentially drastic rise in incidence.

TREATMENT OF TUBERCULOSIS

Drug resistant tuberculosis is transmitted in the same way as regular TB. Primary resistance occurs in persons who are infected with a resistant strain of TB. A patient with fully susceptible TB develops secondary resistance (acquired resistance) during TB therapy because of inadequate treatment, not taking the prescribed regimen appropriately, or using low quality medication. Drug-resistant TB is a public health issue in many developing countries, as treatment is longer and requires more expensive drugs. Multi-drug-resistant tuberculosis (MDR-TB) is defined as resistance to the two most effective first-line TB drugs: rifampicin and isoniazid. Extensively drug-resistant TB (XDR-TB) is also resistant to three or more of the six classes of second-line drugs. The DOTS (Directly Observed Treatment Short-course) strategy of tuberculosis treatment based on clinical trials done in the 1970s by Tuberculosis Research Centre, Chennai, India, focusing on a neglected area of infectious disease control is now showing promising results in effectively treating all TB cases in the community. With treatment, the chances of full recovery is good. Although several treatment protocols for active TB are in wide use by specialists, and protocols sometimes change due to advanced in our understanding of optimal therapy, they generally share three principles:

- ❖ The regimen must include several drugs to which the organisms are susceptible.
- ❖ The patient must take the medication on a regular basis.
- ❖ Therapy must continue for a sufficient time.

Also, treatment recommendations are subject to change depending upon both the characteristics of the particular organism being treated and newer advances in therapeutic agents. Thus, consultation on treatment strategies with local public health and infectious disease experts is always advisable. Isoniazid (INH) is one of the most common drugs used for TB. Inexpensive, effective and easy to take, it can prevent most cases of TB and, when used in conjunction with other drugs, cure most TB. INH preventive treatment is recommended for individuals who have:

- ❖ close contact with a person with infectious TB
- ❖ positive tuberculin skin test reaction and an abnormal chest x-ray that suggests inactive TB
- ❖ a tuberculin skin test that converted from negative to positive within the past two years
- ❖ a positive skin test reaction and a special medical condition (for example, AIDS or HIV infection or diabetes) or who are on corticosteroid therapy
- ❖ a positive skin test reaction, even with none of the above risk factors (in those under 35)

Isoniazid and rifampin are the keystones of treatment, but because of increasing resistance to them, pyrazinamide and either streptomycin sulfate or ethambutol HCL are added to regimens. If the patient is unable to take pyrazinamide, a nine-month regimen of isoniazid and rifampin is recommended. Even if susceptibility testing reveals that the patient is infected with an isoniazid-resistant strain, the isoniazid component is continued because

some organisms may yet be sensitive. In addition, two drugs to which the organisms are likely to be sensitive also are incorporated into the regimen. The beginning phase of treatment is crucial for preventing the emergence of drug resistance and ensuring a good outcome. Six months is the minimum acceptable duration of treatment for all adults and children with culture-positive TB. Drug resistance may be either primary or acquired. Primary resistance occurs in patients who have had no previous antimycobacterial treatment. Acquired resistance occurs in patients who have been treated in the past, and it is usually is a result of non-adherence to the recommended regimen or incorrect prescribing. It has been estimated that one in seven cases of tuberculosis is resistant to drugs that previously cured the disease. Resistance arises when patients fail to complete their drug therapy, lasting six months or longer. The hardiest TB bacteria are allowed to survive as a result, and as they multiply, they spread their genes to a new generation of bacteria - and to new victims. The drug-resistant forms of TB that do not respond to the usual drug therapy might be treatable by other, sometimes more toxic drugs. Officials of the Center for Disease Control and Prevention call for aggressive intervention to prevent the further spread of drug-resistant TB, including finding "every TB patient" and ensuring that patients complete their drug therapy. To accomplish this, increasing use of directly observed therapy (DOT) is being used - that is, the actual, documented observation of the patient when he or she takes the medicine. This method has been shown to reduce the likelihood of treatment failures. Overall, it is critical to consult with a physician about the optimal course of therapy for any given case of tuberculosis. In turn, your physician will likely consult with local public health experts to determine if any local circumstances (such as drug-resistant TB) apply to a particular case.

Antibiotic	Side effects
Isoniazid	Hepatitis, peripheral neuropathy, central nervous system effects including seizures, psychosis, encephalopathy
Pyrazinamide	Arthralgia, hyperuricemia, hepatitis, photosensitivity, gastric irritation; contraindicated in pregnant patients
Rifampin	Drug interactions; gastric irritation; colitis; fever; puritis; anaphylaxis; thrombocytopenia; leukopenia; hemolytic anemia; elevated LFT (liver function test); flu-like symptoms; colors body fluids orange; may permanently discolor contact lenses
Streptomycin	Ototoxicity, paresthesia, dizziness, nausea, tinnitus, nephrotoxicity, peripheral neuropathy, allergic skin rash
Ethambutol	Optic neuritis, peripheral neuropathy, headache, rashes, arthralgias, hyperuricemia, anaphylaxis (rare)

HOME TREATMENT

Home treatment for tuberculosis (TB) focuses on taking the medications correctly to reduce the risk of developing multidrug-resistant TB. Keep all your medical appointments, take

your medications as prescribed, and report any side effects of the medications, especially vision problems. If you plan to move during the time that you are being treated, let your health professional know so that arrangements can be made for you to continue the treatment.

Home treatment includes:

- ❖ Not going to work or school while you can spread the TB infection. Sleep in a bedroom by yourself until you can no longer infect other people.
- ❖ Opening windows in a room where you must stay for a while, if the weather allows it. This can help get rid of TB bacteria from the air in the room.
- ❖ Eating a balanced diet to provide your body with the nutrients that you need to fight the infection. If you need help, ask to talk with a registered dietitian.
- ❖ Covering your mouth when you sneeze or cough. Until you have been on antibiotics for about 2 weeks, you can easily spread the disease to others. After coughing, dispose of the soiled tissue in a covered container. Talk with your health professional about other precautions you can take to prevent the spread of TB.

CONCLUSION

Daily oral doses are continued for 1 year or longer. Directly observed therapy, in which a health care provider watches the patient take the prescribed antitubercular drugs, is the

most effective strategy for some patients. In this case, drugs may be given 2 or 3 times per week, as prescribed by a doctor. Tuberculosis is largely a preventable disease. In the United States, doctors try to identify persons infected with *M. tuberculosis* as early as possible, before they have developed active tuberculosis. They will give a drug called isoniazid (INH) to prevent the active disease. This drug is given every day for 6 to 12 months. INH can cause hepatitis in a small percentage of patients, especially those older than 35 years. A nurse may watch the patients take their medicine to make sure all pills are taken. Hospitals and clinics can take precautions to prevent the spread of tuberculosis. Precautions include using ultraviolet light to sterilize the air, special filters, and special respirators and masks. Until they can no longer spread the tuberculosis germs, tuberculosis patients in hospitals should be isolated in special rooms with controlled ventilation and airflow. For atypical tuberculosis infections, or drug-resistant strains, other drugs may be used to treat the infection. Treatment starts with a minimum of three drugs. Hospitalization may be necessary to prevent spreading the disease to others until the infectious period is over, usually 2-4 weeks after the start of therapy. People can continue their normal activities after the infectious period. With appropriate antibiotic treatment, tuberculosis can be cured in more than nine out of ten patients. Successful tuberculosis treatment depends on close cooperation between the patient and doctor and other health care workers. Tuberculosis treatment usually combines several different antibiotic drugs which are given for at least six months, sometimes for as long as 12 months. Patients must take their medicine on time every day for the 6 to 12 months. Some tuberculosis patients stop taking their prescribed medicines because they may feel better after only a couple of weeks of treatment. Another reason they may stop taking their medicine is because tuberculosis drugs can have unpleasant side effects.

REFERENCE

1. David W. Tschanz, MSPH, PhD (August 2003). "Arab Roots of European Medicine", *Heart Views* 4 (2).
2. Pliny the Elder, Natural History, quoted at Naphtali Lewis, Meyer Reinhold. "Roman Civilization".
3. Who Named It? Léon Charles Albert Calmette. Retrieved on 6 October 2006.
4. Trail R (1970). "Richard Morton (1637–1698)". *Med Hist* 14 (2): 166–74. PMID 4914685.
5. Zur Pathogenie der Impetigines. Auszug aus einer brieflichen Mitteilung an den Herausgeber. [Müller's] *Archiv für Anatomie, Physiologie und wissenschaftliche Medicin*. 1839, page 82.
6. Lahart CJ (2005). Tuberculosis and other mycobacterial diseases. In RE Rakel, ET Bope, eds., *Conn's Current Therapy 2005*. pp. 315–321. Philadelphia: Elsevier Saunders.

7. Ludvigsson JF, et al. (2007). Coeliac disease and risk of tuberculosis: A population based cohort study. *Thorax*, 62(1): 23–28.
8. Centers for Disease Control and Prevention (2005). Guidelines for using the QuantiFERON®-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. *MMWR*, 54(RR-15): 49–55.
9. Centers for Disease Control and Prevention (2002). *CDC's Response to Ending Neglect: The Elimination of Tuberculosis in the United States*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
10. Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention (2005). Questions and Answers About TB. Available online: <http://www.cdc.gov/nchstp/tb/faqs/qa.htm>.
11. American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America (2003). Treatment of tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 167(4): 603–662.
12. Fitzgerald D, Haas DW (2005). *Mycobacterium tuberculosis*. In GL Mandell et al., eds., *Principles and Practice of Infectious Diseases*, 6th ed., pp. 2852–2886. Philadelphia: Elsevier.