Recent trends of drug used treatment of tuberculosis

[1]Debjit Bhowmik*, Chiranjib ,[2] R.Margret Chandira, B.Jayakar, [3]K.P.Sampath Kumar

1. Rajiv Gandhi College of Pharmacy, Uttar Pradesh
2.Vinayaka missions college of Pharmacy, Salem
3.Coimbatore medical college, Coimbatore, Tamilnadu

Abstract

Tuberculosis 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. Even better, people with latent TB infection can take medicine so that they will not develop active TB disease. Isoniazid and rifampin are the keystones of treatment, but because of increasing resistance to them, pyrazinamide and either streptomycin sulfate or ethambutol HCL is 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. Tuberculosis is a highly infectious life-threatening bacterial disease with 8 million new cases and 3 million deaths reported worldwide each year to the World Health Organization.

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.Tuberculosis is either latent or active.Latent TB means that you have the TB bacteria in your body, but your body's defenses (immune system) fight the infection and try to

keep it from turning into active TB. This means that you don't have any symptoms of TB right now and can't spread the disease to others. If you have latent TB, it can become active TB. Active TB means that the TB bacteria are growing and causing symptoms. If your lungs are infected with active TB, it is easy to spread the disease to others. Pulmonary TB (in the lungs) is contagious. It spreads when a person who has active TB breathes out air that has the TB bacteria in it and then another person breathes in the bacteria from the air. An infected person releases even more bacteria when he or she does things like cough or laugh.If TB is only in other parts of the body (extrapulmonary TB), it does not spread easily to others.TB is a preventable disease, even in those who have been exposed to an infected person. Skin testing (PPD) for TB is used in high risk populations or in people who may have been exposed to TB, such as health care workers. A positive skin test indicates TB exposure and an inactive infection. Discuss preventive therapy with your doctor. People who have been exposed to TB should be skin tested immediately and have a follow-up test at a later date, if the first test is negative. Prompt treatment is extremely important in controlling the spread of TB from those who have active TB disease to those who have never been infected with TB.Some countries with a high incidence of TB give people a BCG vaccination to prevent TB.The goal of treatment is to cure the infection with drugs that fight the TB bacteria. Treatment of active pulmonary TB will always involve a combination of many drugs (usually four drugs). It is continued until lab tests show which medicines work best. You may need to take many different pills at different times of the day. This may be difficult for some people. However, it is very important that you take the pills the way your health care provider instructed. When people do not take their tuberculosis medications as recommended, the infection becomes much more difficult to treat. Sometimes, the drugs no longer help treat the infection 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. 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. 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. Standard therapy for active TB consists of a six-month regimen: two months with Rifater (isoniazid, rifampin, and pyrazinamide),four months of isoniazid and rifampin (Rifamate, Rimactane) ethambutol (Myambutol) or streptomycin added until your drug sensitivity is known (from the results of bacterial cultures) . 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. Drug-resistant tuberculosis, particularly that caused by strains resistant to isoniazid and rifampin, is much harder to treat and often is fatal. Ethambutol is indicated in combination with other antituberculosis medications in the treatment of all forms of tuberculosis, including tuberculous meningitis, caused by Mycobacterium tuberculosis. A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide is recommended in the initial phase of short-course therapy which is usually continued for 2 months. 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.

Causes of Tuberculosis

Tuberculosis infection can develop after inhaling droplets sprayed into the air from a cough or sneeze by someone infected with the *Mycobacterium tuberculosis* bacteria. Small areas of infection, called granulomas (granular tumors), develop in the lungs.The usual site of tuberculosis is the lungs, but other organs can be involved. In the U.S., most people with primary tuberculous get better and have no further evidence of disease. Disseminated disease develops in the small number of infected people whose immune systems do not successfully contain the primary infection. Disseminated disease can occur within weeks after the primary infection, or may lie dormant for years before causing illness. Infants, the elderly, and those infected with HIV are at higher risk for the disease worsening, because of their weaker immune systems.In disseminated disease, organs and tissues affected can include:

- Bones and joints
- Bronchus
- Cervical lymph nodes
- Eye
- Larynx (voice box)
- Lining of the abdominal cavity (peritoneum)
- Lining of the brain and spinal cord (meninges)
- Lining of the heart (pericardium)
- Organs of the male or female urinary and reproductive systems
- Skin
- Small bowel
- Stomach

The risk of catching TB increases when you are in contact with people who have the disease, if you live in crowded or unsanitary conditions, and if you have poor nutrition. Recently, TB has been seen more often in the U.S. Factors that may be causing this increase are tuberculosis infections in people with AIDS and HIV, and increasing numbers of homeless people. Another matter of concern is the development of drug-resistant strains of TB. Incomplete treatment of TB infections (such as not taking medications for the prescribed length of time) can contribute to the development of drug-resistant strains of bacteria. About half of AIDS patients with a CD4 count less than 200 who develop TB will have disseminated disease (not localized disease, as in lung tuberculosis).

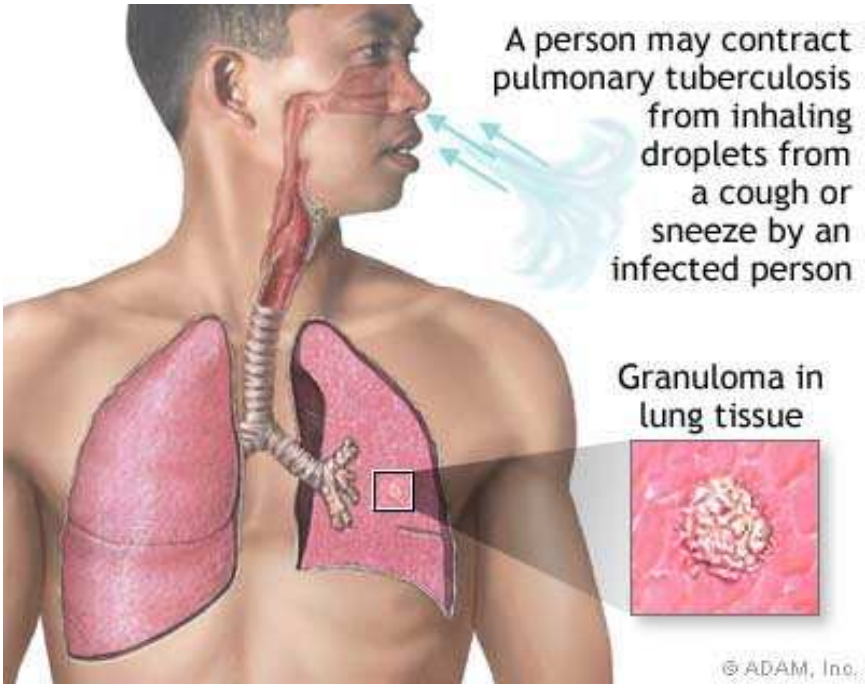

Figure-1 Pulmonary Tuberculosis in lung

Risk for TB

Some people are more likely than others to get TB. This includes people who:

- Have HIV or another illness that weakens their immune system.
- Have close contact with someone who has active TB, such as living in the same house as someone who is infected with TB.
- Care for a patient who has active TB, such as doctors or nurses.
- Live or work in crowded places such as prisons, nursing homes, or homeless shelters, where other people may have active TB.
- Have poor access to health care, such as homeless people and migrant farm workers.
- Abuse drugs or alcohol.
- Travel to or were born in places where untreated TB is common, such as Latin America, Africa, Asia, Eastern Europe, and Russia.

It is important for people who are at a high risk for getting TB to get tested once or twice every year.

Symptoms of Tuberculosis

Most of the time when people are first infected with TB, the disease is so mild that they don't even know they have it. People with latent TB don't have symptoms unless the disease becomes active.

Symptoms of active TB may include:

- A cough that brings up thick, cloudy, and sometimes bloody mucus from the lungs (called sputum) for more than 2 weeks.
- Tiredness and weight loss.

- Night sweats and a fever.
- A rapid heartbeat.
- Swelling in the neck (when lymph nodes in the neck are infected).
- Shortness of breath and chest pain (in rare cases).

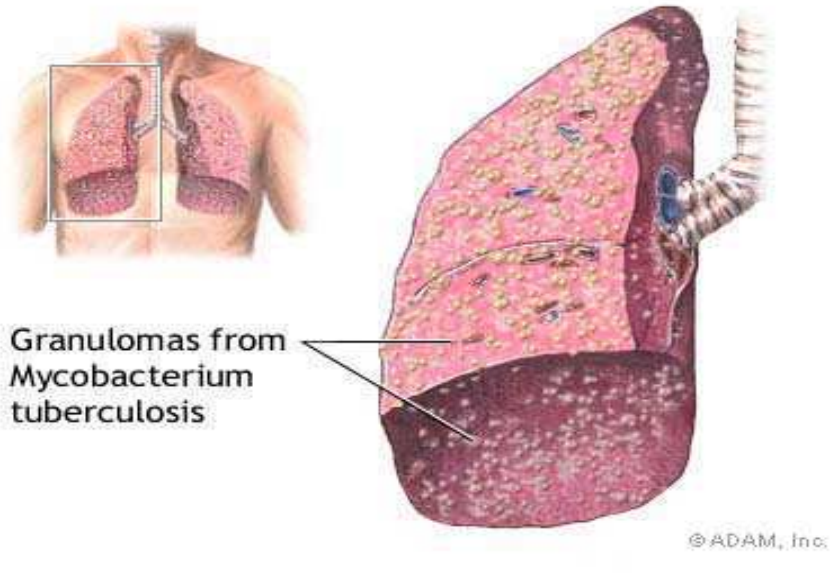

Figure-2 Mycobacterium Tuberculosis

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 X-rays. 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. [3] 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.
- *Diagnosing TB outside the lungs*
- Diagnosing TB in other parts of the body (extrapulmonary TB) requires more testing. You may have:
- A sample of the affected area taken out (biopsy). The sample is sent to a lab to look for TB-causing bacteria.
- A urine culture to look for TB infection in the kidneys (renal TB).
- A sample of fluid around the spine (cerebrospinal fluid) taken to look for a TB infection in the brain (TB meningitis).
- A CT scan to diagnose TB that has spread throughout the body (miliary TB) and to detect lung cavities caused by TB.
- An MRI scan to look for TB in the brain or the spine.
- Testing for HIV infection is often done at the time of TB diagnosis. You may also have a blood test for hepatitis. [4]

Tests during TB treatment

During treatment, sputum tests are done once a month or more often to make sure the antibiotics are working. You may have a chest X-ray at the end of treatment to use as a comparison in the future. You may have tests to see if TB medications are harming other parts of your body. These tests may include:

- Liver function tests.
- Eye tests, especially if you are taking ethambutol for TB treatment.
- Hearing tests, especially if you are taking streptomycin for TB treatment.

Early Detection

All cases of TB are reported to the local or state health department because the disease can spread to others and cause outbreaks. Major health authorities keep track of TB outbreaks and encourage early testing for people who are at risk for developing the disease.The Centers for Disease Control and Prevention (CDC) recommend TB testing for people who:

- Have a human immunodeficiency virus (HIV) infection or another condition that puts them at risk for TB.
- Spend a lot of time with a person who has active TB disease, which can be spread to others.
- Inject illegal drugs.
- Were born in parts of the world where tuberculosis is common, such as Latin America and the Caribbean, Africa, Asia, Eastern Europe, and Russia.
- Live or work in nursing homes, homeless shelters, migrant farm camps, prisons, or jails.

People who have a high risk for developing TB usually have a skin test (tuberculin test) on a regular basis. Health professionals often are given a tuberculin skin test when they begin work in a hospital or nursing home, with retesting every 6 to 12 months.

Tuberculosis Pathology

Mycobacterium tuberculosis is a highly contagious, airborne, rod-shaped organism (bacillus) that thrives on oxygen, grows slowly, and possesses a "waxy" cell wall. The cell wall's structure and function are not well understood but appear to allow the bacteria to survive within immune cells called macrophages (specialized cells that destroy bacteria and viruses). It also provides the organism with a resistant barrier to many common drugs.*M. tuberculosis* is difficult to study in the laboratory. Slow growth makes culturing a lengthy process and colony formation can take several weeks. Also, TB bacilli form clumps, making them difficult to work with and count. Because tuberculosis is a dangerous airborne pathogen, study requires special safety equipment.The bacteria's primary host is the human and infection spreads through direct person-to-person contact. When an infected person talks, coughs, sings, or spits, tiny aerosolized droplets containing bacteria are released into the air and inhaled by uninfected persons. Viable bacteria can remain in the air for a long time.Once the bacteria are inhaled, they are engulfed by macrophages (white blood cells) that are present in the alveoli (the air sacs of the lungs). The bacteria replicate within the macrophages for 2 to 3 weeks before spreading throughout the body. In 95% of cases, the macrophages throughout the body are able to contain the bacteria and no apparent disease is noted. However, the bacteria are not completely destroyed and can remain dormant for years. Granulomas prevent spread of infection by confining bacteria within a compact collection of several types of immune cells and activated macrophages, some of which fuse together. These cells work in various but specific ways to isolate, inhibit the replication of, and destroy the bacteria. At the center of this aggregate, toxic substances released by some of the immune cells create an unfavorable environment for the bacteria and most of them die. The center has a soft, dry, crumbly cheese-like appearance and the granuloma is described as caseated (ka'-see-a'-ted; from the Latin word for cheese, caseus). Granulomas then become dormant and are sealed off by scar tissue. If any bacilli survive, they may reactivate years later. What triggers reactivation is not well understood. Five years or more after infection, the bacteria can activate some immune cells to release a substance that renders host tissue cells sensitive to killing. Other immune cells are activated to release substances that liquefy the bacteria-containing center of the granuloma. When the granuloma and surrounding tissue erode, the liquefied material is discharged into an airway and a cavity (enlarged air space) forms in the lung. Oxygen and carbon dioxide then freely enter the space, and bacilli replicate in enormous numbers, thriving in this now highly favorable environment. Bacilli spread through air passages from cavities to other parts of the lung and larynx. Swallowed sputum may cause lesions in the gastrointestinal (GI) tract (i.e., the alimentary tract or digestive tract).

Types of tuberculosis

Tuberculosis (TB) is divided into two categories: pulmonary and extrapulmonary.

Pulmonary Tuberculosis Types

- Primary Tuberculosis Pneumonia
- Tuberculosis Pleurisy
- Cavitary Tuberculosis
- Miliary TB
- Laryngeal Tuberculosis

Primary tuberculosis pneumonia

This uncommon type of TB presents as pneumonia and is very infectious. Patients have a high fever and productive cough. It occurs most often in extremely young children and the elderly. It is also seen in patients with immunosuppression, such as HIV-infected and AIDS patients, and in patients on long term corticosteroid therapy.

Tuberculosis pleurisy

This usually develops soon after initial infection. A granuloma located at the edge of the lung ruptures into the pleural space, the space between the lungs and the chest wall. Usually, a couple of tablespoons of fluid can be found in the pleural space. Once the bacteria invade the space, the amount of fluid increases dramatically and compresses the lung, causing shortness of breath (dyspnea) and sharp chest pain that worsens with a deep breath (pleurisy). A chest x-ray shows significant amounts of fluid. Mild- or low-grade fever commonly is present. Tuberculosis pleurisy generally resolves without treatment; however, two-thirds of patients with tuberculosis pleurisy develop active pulmonary TB within 5 years.

Cavitary TB

Cavitary TB involves the upper lobes of the lung. The bacteria cause progressive lung destruction by forming cavities, or enlarged air spaces. This type of TB occurs in reactivation disease. The upper lobes of the lung are affected because they are highly oxygenated (an environment in which *M. tuberculosis* thrives). Cavitary TB can, rarely, occur soon after primary infection.

Symptoms include productive cough, night sweats, fever, weight loss, and weakness. There may be hemoptysis (coughing up blood). Patients with cavitary TB are highly contagious. Occasionally, disease spreads into the pleural space and causes TB empyema (pus in the pleural fluid).

Miliary TB

Miliary TB is disseminated TB. "Miliary" describes the appearance on chest x-ray of very small nodules throughout the lungs that look like millet seeds. Miliary TB can occur shortly after primary infection. The patient becomes acutely ill with high fever and is in danger of dying. The disease also may lead to chronic illness and slow decline.

Symptoms may include fever, night sweats, and weight loss. It can be difficult to diagnose because the initial chest x-ray may be normal. Patients who are immunosuppressed and children who have been exposed to the bacteria are at high risk for developing miliary TB.

Laryngeal TB

TB can infect the larynx, or the vocal chord area. It is extremely infectious.

Extrapulmonary Tuberculosis

This type of tuberculosis occurs primarily in immunocompromised patients.

- Lymph Node Disease
- Tuberculosis Peritonitis

- Tuberculosis Pericarditis
- Osteal Tuberculosis
- Renal Tuberculosis
- Adrenal Tuberculosis
- Tuberculosis Meningitis

Lymph node disease
Lymph nodes contain macrophages that capture the bacteria. Any lymph node can harbor uncontrolled replication of bacteria, causing the lymph node to become enlarged. The infection can develop a fistula (passageway) from the lymph node to the skin.

Tuberculosis peritonitis
M. tuberculosis can involve the outer linings of the intestines and the linings inside the abdominal wall, producing increased fluid, as in tuberculosis pleuritis. Increased fluid leads to abdominal distention and pain. Patients are moderately ill and have fever.

Tuberculosis pericarditis
The membrane surrounding the heart (the pericardium) is affected in this condition. This causes the space between the pericardium and the heart to fill with fluid, impeding the heart's ability to fill with blood and beat efficiently.

Osteal tuberculosis
Infection of any bone can occur, but one of the most common sites is the spine. Spinal infection can lead to compression fractures and deformity of the back.

Renal tuberculosis
This can cause asymptomatic pyuria (white blood cells in the urine) and can spread to the reproductive organs and affect reproduction. In men, epididymitis (inflammation of the epididymis) may occur.

Adrenal tuberculosis
TB of the adrenal glands can lead to adrenal insufficiency. Adrenal insufficiency is the inability to increase steroid production in times of stress, causing weakness and collapse.

TB meningitis
M. tuberculosis can infect the meninges (the main membrane surrounding the brain and spinal cord). This can be devastating, leading to permanent impairment and death. TB can be difficult to discern from a brain tumor because it may present as a focal mass in the brain with focal neurological signs.
Headache, sleepiness, and coma are typical symptoms. The patient may appear to have had a stroke.

Recent trends in tuberculosis drug therapy
Treatment of active TB is complex and is becoming even more complex with the emergence of multidrug-resistant tuberculosis and HIV infection. Hospital admission is recommended for severe cases.Standard therapy for pulmonary TB includes isoniazid and rifampin for 6 months

along with pyrazidamide for the first 2 months (isoniazid and rifampin without pyrazidamide may be used for 9 months, if necessary). Treatment consists of three drugs that are effective against the organism. If the incidence of drug-resistant TB in a community is greater than 4%, ethambutol or streptomycin is added until sensitivities are known. (All strains of bacteria are tested to determine the sensitivity to the antibiotics used.) Sputum should be negative after 3 months of therapy. If not, treatment is reevaluated. If a patient is unable to tolerate isoniazid, or if isoniazid-resistant TB is present, rifampin, ethambutol, and pyrazidamide are usually used for 18 months. If rifampin-resistant TB is present, the regimen usually consists of isonizaid, ethambutol, and pyrazidamide for 18 months. If there is resistance to both isoniazid and rifampin, the disease is very difficult to treat.

Table-1 Antibiotics and its side effects

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)

Standard therapy for extrapulmonary TB

Therapy for extrapulmonary TB uses the same drugs but may last longer. Steroid therapy may be useful in pericardial disease and is indicated in children with meningitis.

Surgery

With multidrug-resistant TB that does not respond to antibiotics, the infected portion(s) of the lung may be removed surgically. The prognosis for these patients is extremely poor. Tuberculosis empyema (pus in pleural fluid) may require chesttube drainage of the pleural space.

Treating pregnant patients

Pregnant patients with TB usually receive isonizaid and rifampin with ethambutol. These drugs have not been found to be harmful to the fetus. Streptomycin is contraindicated because it causes deafness in the fetus. Pyrazinamide is also contraindicated in pregnant patientsWith 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:

1. The regimen must include several drugs to which the organisms are susceptible.
2. The patient must take the medication on a regular basis.

3. 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.

Doctors treat tuberculosis (TB) with antibiotics to kill the TB bacteria. These medications are given to everyone who has TB, including infants, children, pregnant women, and people who have a system. People who have TB that cannot be spread to others (latent TB) also receive

treatment to prevent the infection from becoming active.When treating active TB, health experts recommend:

- Using more than one medication to prevent multidrug-resistant TB. The standard treatment begins with four medications given for 2 months.
- Continuing treatment for 4 to 9 months or longer if necessary. The number of medicines used during this time depends on the results of sensitivity testing.
- Using directly observed therapy (DOT). This means visits with a health professional who watches you every time you take your medication. A cure for TB requires you to take all doses of the antibiotics. These visits ensure that people follow medication instructions, which is helpful because of the long treatment course for TB.
- Trying a different combination of medications if the treatment is not working because of drug resistance (when tests show that TB-causing bacteria are still active).
- Using different treatment programs for people infected with the human immunodeficiency virus (HIV), people infected with TB bacteria that are resistant to one or more medicines, pregnant women, and children.
- When treating latent TB, experts recommend: Using one medicine to kill the TB bacteria and prevent active TB. The standard treatment is isoniazid taken for 9 months. For people who cannot take isoniazid for 9 months, sometimes a 6-month treatment program is done.
- Treatment with rifampin for 4 months. This is an acceptable alternate treatment, especially for people who have been exposed to bacteria that is resistant to isoniazid.

Treatment for extrapulmonary tuberculosis

Treatment for tuberculosis outside the lungs (extrapulmonary TB) usually is the same as for pulmonary TB. You may need other medications or forms of treatment depending on where the infection is in the body and whether complications develop.

You may need treatment in a hospital if you have:

- Severe symptoms.
- TB that is resistant to multiple-drug therapy.
-

Medications are the cornerstone of tuberculosis treatment. But treating TB takes much longer than treating other types of bacterial infections. Normally, you take antibiotics for at least six to nine months to destroy the TB bacteria. The exact drugs and length of treatment depend on your age, overall health, possible drug resistance, the form of TB (latent or active) and its location in the body.

Several promising new TB drugs are in development, and some may become available within the next 10 years.

Treating TB infection (latent TB)

If tests show that you have TB infection but not active disease, your doctor may recommend preventive drug therapy to destroy bacteria that might become active in the future. You're likely to receive a daily or twice-a-week dose of the TB medication isoniazid. For treatment to be effective, you usually take isoniazid for nine months. Long-term use of isoniazid can cause side effects, including the life-threatening liver disease hepatitis. For this reason, your doctor will

monitor you closely while you're taking isoniazid. During treatment, avoid using acetaminophen (Tylenol, others) and avoid or limit alcohol use. Both increase your risk of liver damage.

Treating active TB disease

If you're diagnosed with active TB, you're likely to begin taking four medications — isoniazid, rifampin (Rifadin), ethambutol (Myambutol) and pyrazinamide. This regimen may change if tests later show some of these drugs to be ineffective. Even so, you'll continue to take several medications. Depending on the severity of your disease and whether the bacteria are drug-resistant, one or two of the four drugs may be stopped after a few months. You may be hospitalized for the first two weeks of therapy or until tests show that you're no longer contagious.

Sometimes the drugs may be combined in a single tablet such as Rifater, which contains isoniazid, rifampin and pyrazinamide. This makes your treatment less complicated while ensuring that you get all the drugs needed to completely destroy TB bacteria. Another drug that may make treatment easier is rifapentine (Priftin), which is taken just once a week during the last four months of therapy, in combination with other drugs.

Medication side effects

Side effects of TB drugs aren't common, but can be serious when they do occur. All TB medications can be highly toxic to your liver. Rifampin can also cause severe flu-like signs and symptoms — fever, chills, muscle pain, nausea and vomiting. When taking these medications, call your doctor immediately if you experience any of the following:

1) Nausea or vomiting
2) Loss of appetite
3) A yellow color to your skin (jaundice)
4) Dark urine
5) A fever that lasts three or more days and has no obvious cause
6) Tenderness or soreness in your abdomen
7) Blurred vision or colorblindness

Treating drug-resistant TB

Multidrug-resistant TB (MDR TB) can't be cured by the two major TB drugs, isoniazid and rifampin. Extensive drug-resistant TB (XDR TB) is resistant to those drugs as well as three or more of the second line TB drugs. Treating these resistant forms of TB is far more costly than is treating nonresistant TB.Treatment of drug-resistant TB requires taking a "cocktail" of at least four drugs, including first line medications that are still effective and several second line medications, for 18 months to two years or longer. Even with treatment, many people with these types of TB may not survive. If treatment is successful, you may need surgery to remove areas of persistent infection or repair lung damage.

Treating people who have HIV/AIDS

HIV-positive people are especially likely to develop active TB, and drug-resistant forms of the disease are especially dangerous for them. What's more, the most powerful AIDS drugs (antiretroviral therapy) interact with rifampin and other drugs used to treat TB, reducing the effectiveness of both types of medications.

To avoid interactions, people living with both HIV and TB may stop taking antiretroviral therapy while they complete a short course of TB therapy that includes rifampin. Or they may be treated with a TB regimen in which rifampin is replaced with another drug that's less likely to interfere with AIDS medications. In such cases, doctors carefully monitor the response to therapy, and the duration and type of regimen may change over time.

Treating children and pregnant women

Treating TB in children is largely the same as treating adults, except that ethambutol is not used for young children because of the possible side effect of vision problems. Instead of ethambutol, children may take streptomycin.For pregnant women with active TB, initial treatment often involves three drugs — isoniazid, rifampin and ethambutol. Pyrazinamide isn't recommended because its effect on the unborn baby isn't known. Some second line TB medications also aren't recommended.

Completing treatment is essential

After a few weeks, you won't be contagious and you may start to feel better. It might be tempting to stop taking your TB drugs. But it is crucial that you finish the full course of therapy and take the medications exactly as prescribed by your doctor. Stopping treatment too soon or skipping doses can allow the bacteria that are still alive to become resistant to those drugs, leading to TB that is much more dangerous and difficult to treat. Drug-resistant strains of TB can quickly become fatal, especially if your immune system is impaired.In an effort to help people stick with their treatment, a program called directly observed therapy (DOT) is recommended. In this approach, a nurse or other health care professional administers your medication so that you don't have to remember to take it on your own. Sometimes clinics provide incentives, such as food coupons or transportation, for people to show up for their appointments.

High-Risk Populations

The elderly

Tuberculosis is more common in elderly persons. More than one-fourth of the nearly 23,000 cases of TB reported in the United States in 1995 developed in people above age 65. Many elderly patients developed the infection some years ago when the disease was more widespread. There are additional reasons for the vulnerability of older people: those living in nursing homes and similar facilities are in close contact with others who may be infected. The aging process itself may weaken the body's immune system, which is then less able to ward off the tubercle bacillus. Finally, bacteria that have lain dormant for some time in elderly persons may be reactivated and cause illness.

Racial and ethnic groups

TB also is more common in blacks, who are more likely to live under conditions that promote infection. As the end of the century approaches, two-thirds of all cases of TB in the United States affect African Americans, Hispanics, Asians, and persons from the Pacific Islands. Another one-fourth of cases affect persons born outside the United States. As of 1992, the risk of TB was still increasing in all these groups.

Life style factors.

The high risk of TB in AIDS patients extends to those infected by human immunodeficiency virus (HIV) who have not yet developed clinical signs of AIDS. Alcoholics and intravenous drug abusers are also at increased risk of contracting tuberculosis. Until the economic and social factors that influence the spread of tubercular infection are remedied, there is no real possibility of completely eliminating the disease.

Prevention

In general, TB is preventable. From a public health standpoint, the best way to control TB is to diagnose and treat people with TB infection before they develop active disease and to take careful precautions with people hospitalized with TB. But there also are measures you can take on your own to help protect yourself and others:

*Keep your immune system healthy***.** Eat plenty of healthy foods including fruits and vegetables, get enough sleep, and exercise at least 30 minutes a day most days of the week to keep your immune system in top form.

*Get tested regularly***.** Experts advise people who have a high risk of TB to get a skin test once a year. This includes people with HIV or other conditions that weaken the immune system, people who live or work in a prison or nursing home, health care workers, people from countries with high rates of TB, and others in high-risk groups.

*Consider preventive therapy***.** If you test positive for latent TB infection, your doctor will likely advise you to take medications to reduce your risk of developing active TB. Vaccination with BCG isn't recommended for general use in the United States, because it isn't very effective in adults and it causes a false-positive result on a Mantoux skin test. But the vaccine is often given to infants in countries where TB is more common. Vaccination can prevent severe TB in children. Researchers are working on developing a more effective TB vaccine.

*Finish your entire course of medication***.** This is the most important step you can take to protect yourself and others from TB. When you stop treatment early or skip doses, TB bacteria have a chance to develop mutations that allow them to survive the most potent TB drugs. The resulting drug-resistant strains are much more deadly and difficult to treat.
To help keep your family and friends from getting sick if you have active TB:

*Stay home***.** Don't go to work or school or sleep in a room with other people during the first few weeks of treatment for active TB.

*Ensure adequate ventilation***.**
Open the windows whenever possible to let in fresh air.
*Cover your mouth***.** It takes two to three weeks of treatment before you're no longer contagious. During that time, be sure to cover your mouth with a tissue anytime you laugh, sneeze or cough. Put the dirty tissue in a bag, seal it and throw it away. Also, wearing a mask when you're around other people during the first three weeks of treatment may help lessen the risk of transmission.

Home remedies for tuberculosis

The chief therapeutic agent needed for the treatment of tuberculosis is calcium. Milk is the richest food source for the supply of organic calcium to the body and should be taken liberally. In fact an exclusive milk diet is considered highly valuable in tuberculosis. However, a preparatory fast for three days, consisting of raw juices, preferably, orange juice, is essential before the milk diet is begun. The procedure is to take half a glass of orange juice diluted with an equal quantity of water every two hours from 8 a.m. to 8 p.m. For the full milk diet, the patient should have a glass of milk every two hours from 8 a.m. to 8 p.m. on the first day, followed by a glass and a half every hour on the second day. Thereafter, the quantity can be gradually increased until the patient takes a glass every half an hour. Usually, six litres of milk should be taken every day. In the case of women, five litres should be sufficient. Raw milk, that is, milk, which has not been pasteurised, produces the best results, provided it is clean and pure. Milk should be kept cool and away from dust, flies, odours, and sunlight. It should be gently stirred before use to ensure an even distribution of cream. It should be sipped very slowly so as to be thoroughly mixed with saliva which dilutes it and, to a great extent, promotes its digestion. Nearly eight to six weeks of a full milk diet is necessary for the success of the treatment. A considerable amount of rest is necessary with a milk diet and the patient should lie down for about two hours twice a day.

Tuberculosis treatment using Custard Apple

Custard apple is regarded as one of the most valuable remedies for tuberculosis. It is said to contain the qualities of rejuvenating drugs. Ayurvedic practitioners prepare a fermented liquor called sitaphalasava from this fruit, when in season, for use as a medicine in the treatment of this disease. The pulp of two custard apples and twenty-five seedless raisins should be boiled in water on a slow fire. When about one-third of the water is left, it should be filtered, and then mixed with two teaspoons of powdered sugar candy, and a quarter teaspoon each of the powder of cardamom, cinnamon, and certain other condiments.

Tuberculosis treatment using Indian Gooseberry

The Indian gooseberry is another valuable remedy for tuberculosis. A tablespoon each of fresh indian gooseberry juice and honey, mixed together, should be taken every morning in treating this disease. Its regular use will promote vigour and vitality in the body within a few days

Tuberculosis treatment using Pineapple

Pineapple juice is beneficial in the treatment of tuberculosis. It has been found to be effective in dissolving mucus and aiding recovery. This juice was used regularly in the past in treating this disease when it was more common than it is at present. One glass of pineapple juice is recommended daily

Tuberculosis treatment using Banana

Bananas are considered useful in tuberculosis. The juice of the plantain or the ordinary cooking bananas works miracles in tile cure of tuberculosis. It claims to have cured patients in an advanced stage of this disease with frequent cough, abundant expectoration and high fever in two months, by this treatment

Tuberculosis treatment using Orange

Oranges are useful in the treatment of tuberculosis. A glass of orange juice should be mixed with a pinch of salt and a tablespoon of honey and taken daily by the patient. Due to its saline action in the lungs, it eases expectoration and protects the body from secondary infections.

Tuberculosis treatment using Drumstick

A soup prepared from drumstick leaves has been found valuable in this disease. This soup is prepared by adding a handful of leaves to 200 ml of water which has been heated to a boiling point. The water should then be allowed to boil for five minutes more. After that it should be removed from the fire and allowed to cool. A little salt, pepper, and lime juice may be added to this soup. This drink should be taken first thing every morning.

Tuberculosis treatment using Bottle Gourd

The use of bottle gourd is considered an effective remedy for tuberculosis. Bottle gourd is one of the best vegetables for tuberculosis patients. Regular use of cooked bottle gourd helps in developing immunity against tubercular germs.

Tuberculosis treatment using Mint

The fresh juice of mint has also been found useful in this disease. A teaspoon of this juice, mixed with two teaspoons of pure malt vinegar and an equal quantity of honey, should be stirred in 120 ml of carrot juice. This should be given as a medicinal tonic thrice daily in the treatment of tuberculosis. It liquefies the sputum, nourishes the lungs, increases body resistance against infection, and prevents the harmful effects of anti-tubercular drugs.

Multi drug therapy in tuberculosis

Multiple-drug therapy to treat TB means taking several different antibiotics at the same time. This is the first choice of treatment for TB that is growing in your body (active TB disease). Most of these medicines are given as pills. The standard treatment is to take isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months. Treatment is then continued for at least 4 months with fewer medicines. Also, there are special treatment recommendations for people with HIV and TB, people with drug-resistant TB, children with active TB, and pregnant women with active TB.Prepared combination medicines, such as Rifater, are usually used when there is a need for fewer numbers of pills, such as when a health professional is not giving each dose of medicine personally. Combining antibiotics into a single pill makes it less likely that you will miss taking any doses. Failure to take a medicine could prolong your treatment and increase your chance of developing drug-resistant TB.Streptomycin usually is given only to people who cannot take ethambutol.Isoniazid given alone usually prevents a latent TB infection from turning into active TB disease, which can spread to other people. Rifampin also can help prevent latent TB from becoming active TB.When multiple-drug therapy combines 4 medications, up to 90% of people have a sputum culture that indicates no infection within 3 months after beginning treatment. For people infected with TB bacteria that can be killed by the medicines used for treatment, 98% are permanently cured if they take the medicines exactly as they should. The cure rate for people who have TB and HIV is similar to that for people who have only TB.It takes at least 6 months of treatment for a cure. It could take longer if doses are missed. It can also take longer if the disease does not respond well to the medication. For most people who have a latent TB infection, taking isoniazid alone reduces the risk of developing active TB disease by up to 80%.

Tuberculosis scenario in India

TB is one of the leading causes of mortality in India- killing -2 persons every three minute, nearly 1,000 every dayThe strategy of Directly Observed Treatment, Short-course (DOTS) is based largely on research done in India in the field of TB over the past 35 years.Since 1997, after successful piloting DOTS has been implemented in India as the Revised National Tuberculosis Control Programme (RNTCP). In the RNTCP, the proportion of TB cases which are confirmed in the laboratory and the cure rate are both more than double that of the previous programme,The operational feasibility of DOTS in the Indian context has been demonstrated, with 8 out of 10 patients treated in the programme being cured, as compared with approximately 3 out of 10 in the previous programme.Multidrug -resistant tuberculosis (MDRTB) is a result and symptom of poor management of TB patients. DOTS has been shown to prevent the emergence of MDRTB and to reverse the trend of MDRTB in communities in which it has emerged.TB is the most common opportunistic infection among people living with HIV.Revised National Tuberculosis Control Programme (RNTCP) has covered the entire population of the country by March 2006. Every patient who is cured stops spreading TB, and every life saved is a child, mother, or father who will go on to live a longer, TB-free life.**I**n 1992, the Government of India, together with the World Health Organization (WHO) and Swedish International Development Agency (SIDA), reviewed the National TB Programme and concluded that it suffered from managerial weakness, inadequate funding, over-reliance on x-ray, non-standard treatment regimens, low rates of treatment completion, and lack of systematic information on treatment outcomes. Programme review showed that only 30% of patients were diagnosed and only 30% of those treated successfully. Based on the findings and recommendations of the review in 1992, the GOI evolved a revised strategy and launched the Revised National TB Control Programme (RNTCP) in the country. Starting as pilots in October 1993, the RNTCP was implemented in a population of 2.35 million in 5 sites in different states (Delhi, Kerala, West Bengal, Maharashtra, and Gujarat). The programme was expanded to a population of 13.85 million in 1995 and 16 million in 1996. Having proved both its technical and operational feasibility, a soft loan of US $ 142 million was negotiated with the World Bank in December 1996 and the credit agreement was signed with IDA in May 1997. In 1997 RNTCP was launched as a national programme. It was envisaged to implement RNTCP in 102 districts of the country covering a population of 271 million in a phased manner. Another 203 SCC districts with a population of 447 million were envisaged to be strengthened as a transitional step for introduction of revised strategy at a later stage. Having started in 1997, rapid scale-up began in late 1998, when another 100 million populations was covered under RNTCP. Starting in 1997, the project was implemented in a phased manner to ensure that quality of services is maintained. By March 2006, entire country has been covered under the programme.Revised National TB Control Programme and its recent progress in DOTS expansion has been encouraging. As per Global TB Report 2003, 2/3rd of the additional sputum positive cases reported under DOTS in 2001, were found in India. In 2002, over 620,000 cases were placed on treatment of which nearly 250,000 were new smear positive cases. In the year 2003, more than 900,000 cases were placed on treatment. In the year 2004 alone more than 1100,000 cases were placed on treatment, and in the 2005, more than 1290,000 cases were placed on treatment - largest cohort of cases, more than any other country in the world . By June 2009, more than 10.2 million patients have been initiated on treatment, saving more than 1.9 million additional lives. The success of DOTS in India has contributed substantially to the success of TB control in the world.RNTCP has consistently achieved treatment success rate of more than 85%, and case detection close to the global target. However,

in 2007 RNTCP for the first time has achieved the global target of 70% case detection while maintaining the treatment success rate of more than 85%.

Conclusion

In those parts of the world where the disease is common, the World Health Organization (WHO) recommends that infants receive a vaccine called BCG made from a live weakened bacterium related to *M. tuberculosis*. BCG vaccine prevents *M. tuberculosis* from spreading within the body, thus preventing tuberculosis from developing. Treatment for TB uses antibiotics to kill the bacteria. The two antibiotics most commonly used are rifampicin and isoniazid. However, instead of the short course of antibiotics typically used to cure other bacterial infections, TB requires much longer periods of treatment (around 6 to 12 months) to entirely eliminate mycobacteria from the body. Latent TB treatment usually uses a single antibiotic, while active TB disease is best treated with combinations of several antibiotics, to reduce the risk of the bacteriadeveloping antibiotic resistance. People with latent infections are treated to prevent them from progressing to active TB disease later in life.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.However, the vaccine has its drawbacks. It does not protect adults very well against tuberculosis. In addition, BCG interferes with the tuberculosis skin test, showing a positive skin test reaction in people who have received BCG vaccine. In countries where BCG vaccine is used, the ability of the skin test to identify persons that are infected with *M. tuberculosis* is limitedDaily 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.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.

References

1) National Committee for Clinical Laboratory Standards, Antimycobacterial Susceptibility Testing. Proposed Standard NCCLS Document M24-P, Vol. 10, No. 10, NNCLS, Villanova, PA, **1990.**
2) National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically -- Third Edition.

Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December **1993.**
3) National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests -- Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December **1993.**
4) Riley LW. Microbiology and pathogenesis of tuberculosis. http://www.uptodate.com/home/index.html. Accessed Dec. 22, **2008.**
5) Pezzella AT, et al. Surgical aspects of thoracic tuberculosis: A contemporary review - Part 1. Current Problems in Surgery. **2008;** 45:675.
6) Summary. In: WHO Report 2008: Global tuberculosis control - Surveillance, planning, financing. World Health Organization. Accessed Dec. 20, **2008.** http://www.who.int/tb/publications/global_report/2008/summary/en/index.html.
7) Bass JB Jr. Patient information: Tuberculosis. http://www.uptodate.com/home/index.html. Accessed Dec. 20, **2008**.
8) Tuberculosis (TB). National Institute of Allergy and Infectious Diseases. http://www3.niaid.nih.gov/topics/tuberculosis/Understanding/WhatIsTB/TBdefinitions.htm. Accessed Dec. 20, **2008**.
9) Tuberculosis. American Lung Association. http://www.lungusa.org/site/apps/nlnet/content3.aspx?c=dvLUK9O0E&b=4294229&ct=5320855. Accessed Dec. 20, **2008**.
10) Tuberculosis fact sheet. American Lung Association. http://www.lungusa.org/site/apps/nlnet/content3.aspx?c=dvLUK9O0E&b=4294229&ct=3052619. Accessed Dec. 20, **2008**.
11) Tuberculosis (TB): Symptoms. National Institute of Allergy and Infectious Diseases.http://www3.niaid.nih.gov/topics/tuberculosis/Understanding/symptoms.htm. Accessed Dec. 20**, 2008**.
12) Tuberculosis: General information. Centers for Disease Control and Prevention. http://www.cdc.gov/tb/pubs/tbfactsheets/tb.htm. Accessed Dec. 20, **2008.**
13) National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Fifth Informational Supplement, NCCLS Document M100-S5, Vol. 14, No. 16, NCCLS, Villanova, PA, December **1994**.
14) Zhang Y. Advances in the treatment of tuberculosis. Clinical Pharmacology & Therapeutics. **2007**;82:595.
15) Menzies D, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection. Annals of Internal Medicine. **2008**;149:689.
16) Lahart CJ . Tuberculosis and other mycobacterial diseases. In RE Rakel, ET Bope, eds., Conn's Current Therapy **2005.** pp. 315–321. Philadelphia: Elsevier Saunders.
17) Ludvigsson JF, et al. . Coeliac disease and risk of tuberculosis: A population based cohort study. Thorax, 62(1): 23–28.
18) Centers for Disease Control and Prevention . Guidelines for using the QuantiFERON®-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. MMWR, 54(RR-15): 49–55.

19) Centers for Disease Control and Prevention . 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.
20) Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention . Questions and Answers About TB. Available online: http://www.cdc.gov/nchstp/tb/faqs/qa.htm.
21) American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America . Treatment of tuberculosis. American Journal of Respiratory and Critical Care Medicine, 167(4): 603–662.
22) Fitzgerald D, Haas DW . *Mycobacterium tuberculosis*. In GL Mandell et al., eds., Principles and Practice of Infectious Diseases, 6th ed., pp. 2852–2886. Philadelphia: Elsevier.
23) Wilkinson D . Drugs for preventing tuberculosis in HIV infected persons. Cochrane Database of Systematic Reviews (1). Oxford: Update Software.
24) Ziganshina L, Garner P . Tuberculosis,. Onlineversion of Clinical Evidence (15): search date July **2005**,1–15.