Tuberculosis (TB) remains the leading cause of mortality from infectious diseases in humans in the world. In contrast to the world situation, the 14,900 cases of TB reported in the USA in 2003 represent the lowest number of cases ever recorded by public health authorities. However, select populations remain at high-risk for the disease, including people born in countries outside the USA with high prevalence of the disease, persons infected with HIV, and homeless individuals.

Following decades of decline, tuberculosis re-emerged in the mid-1980’s across the USA as a major public health crisis, including multi-drug resistant disease. This epidemic was due in large part to the disassembly of the categorical public health infrastructure for TB required to maintain control of the disease. Unfortunately, as policy makers and public health authorities attempt to economize budgets, lessons of the past are forgotten. TB program functions are increasingly assigned to generalist public health divisions and to the private sector, where the principles and complexities of TB control are often not well-understood. Recent outbreaks of TB among homeless persons in Seattle, Washington, and Portland, Maine, provide warning signals; public health officials and policy makers must advocate for the maintenance of the principles of TB control to avoid another national epidemic of this disease.

The complexities in the diagnosis and treatment of tuberculosis infection and disease call for close
cooperation among public health officials, laboratories, and health care providers, especially those who provide care to people at-risk. New diagnostic and epidemiologic tools, new treatment regimens, and advancements in our understanding of the disease process require all stakeholders in TB control to be continually educated and trained in order to maintain expertise and provide optimal care.

Tuberculosis is preventable and treatable, and most epidemics are avoidable. To prevent TB disease, people infected with TB need to be identified, especially those at increased risk for developing disease, including homeless persons and drug abusers. Early recognition and prompt intervention for TB disease is the key to limiting the spread of TB to others.

Mode of Transmission

Tuberculosis is caused by *Mycobacterium tuberculosis*. These bacteria usually infect people via the respiratory tract. A person with pulmonary TB, the most common form of tuberculosis, can cough the organisms into the air, and others who share the air space may inhale the “droplet nuclei” generated by the cough and become infected. TB can infect other parts of the body after it enters through the lungs, but these infections seldom lead to the transmission of organisms to others.

While the infectiousness of each case varies, TB is not highly infectious in general. People who have had prolonged contact with an infectious person are at highest risk of becoming infected, particularly persons with impaired immune systems, sleeping partners, or those who share close air space for several hours. A person with active pulmonary TB is unlikely to continue transmitting the organism to others once proper therapy has been instituted with clinical and bacteriologic improvement for 14 days.

**Tuberculosis Infection**

After a susceptible person inhales the organisms responsible for TB infection, the bacteria begin to multiply in the lungs and then spread through the body via the blood and lymph systems. The body’s immune system eventually controls the TB organisms in most cases. This immune response, called “sensitization,” usually takes from 4-12 weeks. The tuberculin (PPD) skin test and the QuantiFERON (QFT) blood test measure this immune response, or
sensitization, to the TB organism.

A positive PPD skin test or QuantiFERON test documents prior infection with *M. tuberculosis*. Most infected persons carry the infection in its “latent,” or dormant, form called Latent Tuberculosis Infection (LTBI). This infection may not become active until later in life. Others with a positive PPD or QFT test may have active TB disease. Everyone with a positive test should undergo a proper medical evaluation, including a chest radiograph, to rule out active tuberculosis.

The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS) recently published revised guidelines for tuberculin skin testing and for use of the QuantiFERON test. The TB skin test is a highly standardized test; it must be placed and read by persons trained in its application and interpretation. QFT is a laboratory test performed on blood drawn from the patient within 12 hours. Criteria for interpretation of the tuberculin skin test are summarized in Table 1.

Persons infected with TB may occasionally not show a positive PPD skin test or QFT test. Provided enough time has passed for “sensitization” to occur following an exposure to an infectious case (i.e. usually 4-12 weeks), certain conditions such as some malignancies, sarcoidosis, infection with HIV, or the use of immunosuppressive medicines (such as prednisone) may suppress the body’s response to the test. No methods today enable one to determine TB infection in such circumstances; so-called “anergy” skin test panels have been shown to be unreliable and are not recommended.

**Tuberculosis Disease**

Tuberculosis disease usually occurs when a latent infection becomes active. Disease may follow the initial infection if the immune response fails to contain the spread of the organisms from the lungs (see above), especially in young children (less than 5 years of age) or persons with compromised immune systems (such as HIV-infected persons). Most TB disease in the USA today represents re-activation of latent TB infection. Symptoms and signs of TB disease often are not specific and may be overlooked easily. Active pulmonary disease may present with a cough productive of sputum, fevers, weight loss, night sweats, and/or general fatigue. Tuberculosis of the lymphatic system may produce swollen lymph nodes; tuberculous meningitis may present as a change in mental status.

Caregivers should suspect active TB in anyone who exhibits these symptoms and has had:

- a recent close exposure to an active case of infectious TB;
- a history of a positive PPD or QFT test;
- an abnormal chest x-ray that suggests the presence of TB.

The presence of any of the following should increase the suspicion of TB:

- people with impaired immune systems, including those at-risk for infection with HIV;
- recent PPD skin test conversion (now “positive,” with an increase in size of the reaction of 10 mm or more);
- diabetes mellitus or certain malignancies, such as leukemia or lymphoma;
- prolonged treatment with corticosteroids (more than 15 mg prednisone per day or equivalent, for more than 30 days) or other immunosuppressive drugs;
- malnutrition;
- chronic alcoholism;
- recent immigration from a region of the world where TB is endemic.

**Tuberculosis and HIV Infection**

People infected with HIV who are at risk for exposure to tuberculosis are at a high risk for TB disease. People with HIV infection and history of prior TB infection are at high risk to reactivate their latent TB infection (estimated at approximately 7-10% per year). Persons with impaired immunity from HIV who are exposed to an infectious case of TB are at great risk of developing active TB, although that risk has not been quantified.

With early diagnosis and appropriate treatment, TB is curable. However, TB can be fatal, especially in people with untreated, or inadequately-managed, advanced disease. Death also may occur in people with poor immunity whose infections can sometimes proceed unchecked and lead to overwhelming tuberculosis.

**Diagnosis**

The first step in the diagnosis of TB is the suspicion by the provider or the patient for the disease; the disease must be suspected before the appropriate tests are performed to confirm the diagnosis. The clinical picture, including history, signs, symptoms, and chest radiograph, all contribute to establishing a tentative, working diagnosis of TB in the appropriate setting.

The “typical” chest radiograph in pulmonary tuberculosis has infiltrates of the upper lobes (apical
or posterior segments) or the superior segments of the lower lobes of the lungs with occasional cavity formation. Such a chest x-ray should immediately raise the clinician’s suspicion for TB and trigger appropriate actions. However, the radiograph may involve any lobe or segment and may be mistaken for a routine bacterial pneumonia. Many TB cases have been treated inappropriately as community-acquired pneumonia with routine antibiotics for many weeks before TB was suspected and treatment is initiated. The delay in diagnosis created by such errors frequently results in prolonged transmission of TB to others in close environments, such as shelters. Inappropriate treatment of TB with a single antibiotic, such as a fluoroquinolone, which is often used to treat bacterial pneumonias but which also has excellent antituberculosis activity, also may result in drug resistance.

The chest radiograph also may take on other appearances, such as hilar or mediastinal lymphadenopathy or a pleural effusion. Identification of the TB organism by culture of sputum or tissue biopsies confirms a diagnosis of TB. Because microscopic analysis may confuse other organisms with *M. tuberculosis* on stained sputum smears, fluids, or tissues (such as *Mycobacterium avium* complex, a noninfectious but common cause of infection in AIDS patients with poor immune systems), identification of the TB organism by culture is necessary to confirm a diagnosis and guide treatment.

The analysis of smears may not lead to a confirmed diagnosis by itself but can help assess the degree of infectiousness. The more organisms seen on a sputum smear, the more infectious the person is likely to be. In general, persons with 3 negative sputum smears for mycobacteria, taken at least 8 hours apart (with at least 1 sputum obtained as a first-morning specimen), are less likely to be very infectious.

While the laboratory culture of *M. tuberculosis* remains the “gold standard” for the diagnosis of tuberculosis disease, conventional culture may take up to 8 weeks before results are obtained. Newer culture methods using liquid media now enable detection of the growth of *M. tuberculosis* in 7–21 days. Molecular tests that detect *M. tuberculosis* DNA or RNA in samples of respiratory secretions (including sputum) enable confirmation of a diagnosis of TB within hours in certain circumstances; however, these tests do not provide drug susceptibility data that are essential to the management of the disease and hence do not replace the culture entirely as a tool.

Since the laboratory may take weeks to confirm a diagnosis of TB, caregivers should consider isolation of the patient and initiation of multiple drug treatment for TB disease without knowing...
the culture results whenever the disease is strongly suspected. Sometimes a short course of antituberculosis medications leads to a noticeable improvement in a TB suspect’s condition, even when laboratory tests and cultures show no evidence of organisms. This is known as a clinically verified case response.

**Treatment**

A physician familiar with antituberculosis drugs and their side effects should supervise the treatment of TB infection or TB disease.

*Treatment of Latent Tuberculosis Infection (LTBI)*

Formerly termed “preventive therapy,” treatment of LTBI targets persons with TB infection who are not ill with TB but are at-risk of reactivation of their LTBI to develop active TB disease. These people cannot spread TB to others. Treatment of LTBI destroys the residual organisms of the first infection and prevents reactivation TB disease from occurring. In general, the lifetime risk for reactivation TB disease is approximately 10%; however, this risk is greatest in persons recently infected with the organism (i.e. within the first 2 years of initial infection), in infected close contacts of active cases (with a positive PPD skin test or QFT test), in HIV-infected persons, and in young children.

Recent guidelines for Targeted Testing and Treatment of Latent Tuberculosis Infection have been published, and subsequently revised, by the CDC/ATS. Treatment of LTBI usually consists of a 9-month course of a single medication, isoniazid (INH), administered daily. When taken for the full period, this regimen confers greater than 90% protection against reactivation disease. Where there is a high likelihood of infection with a strain of TB resistant to INH, the prescribing provider may substitute rifampin (Rimactane™, Rifadin™) daily for 4 months or use both INH and rifampin (RIF) for 4 months. A CDC/ATS recommendation for a shorter course of treatment, using 2 months of daily RIF plus pyrazinamide (PZA), another first-line antituberculosis medication, has been withdrawn because of severe hepatic side effects associated with the regimen. This regimen should not be used to treat LTBI.

The major side effect of INH and RIF is toxicity to the liver (i.e. drug-induced hepatitis). Clinical liver toxicity from INH is rare, especially in young adults, occurring in less than 1 in 1,000 patients in one study; liver toxicity from RIF is much less common. People older than 35 years, those who abuse alcohol or drugs, and persons with a history of liver disease are at risk for liver toxicity from these medications. People taking either of these medicines should be educated about potential side effects and instructed to stop the medicine and report to their provider immediately should they...
Caregivers should be alert to symptoms of hepatitis in people taking INH or RIF. These may include nausea, vomiting, fever, jaundice, pain or discomfort in the right upper quadrant of the abdomen, or coffee- or tea-colored urine. Blood tests for liver function (AST/ALT) should be taken at baseline and monitored at least monthly in persons at-risk for liver toxicity from these medications. In most cases, persons with active hepatitis should be referred to an expert for further management before treatment of LTBI is initiated. Persons receiving these medications should be monitored by a health care provider at least monthly for signs and symptoms of toxicity and for adherence. No more than a 1 month supply of medications should be given to the patient at monitoring visits. Approximately 20% of people taking INH will increase their AST up to 5 times the upper limit of normal, with no adverse outcome. If these patients have no symptoms or signs of liver toxicity, the medication may be continued with close monitoring. In persons with signs or symptoms of liver toxicity, the medication should be stopped, and the patient should be evaluated as soon as possible. The CDC/ATS guidelines recommend stopping the medication in persons with signs or symptoms of liver toxicity and whose AST is greater than 3 times normal.

INH interacts with phenytoin (Dilantin™), a common seizure medication, increasing serum levels of both drugs. Patients taking Dilantin™ should have levels monitored during INH treatment.

Rifampin increases the metabolism of a number of drugs, including methadone and warfarin (Coumadin™), an anticoagulant drug. Dosages of these medications may have to be increased during therapy with RIF. Also, RIF may accelerate the clearance of hormones used in oral or implant contraceptives, making them ineffective. Women who use such birth control methods should use an alternative form of birth control to avoid pregnancy while taking RIF. Rifampin also may cause an orange discoloration of urine, sweat, tears, semen, or stool. Permanent discoloration of contact lenses may occur. Rifampin also may result in false-positive urine tests for opiate drugs.

Treatment of Tuberculosis Disease

Guidelines for the Treatment of Tuberculosis have been published recently by the CDC/ATS and the Infectious Diseases Society of America (IDSA). Medical treatment of TB disease usually consists of multiple drugs administered daily or intermittently for at least 6 months. The standard recommended treatment regimen includes 4 antituberculosis drugs: INH, RIF, PZA, and either ethambutol (EMB) or streptomycin (SM) given daily for 2 months (60 doses), followed by 4 months of 2 drugs (usually INH + RIF; 120 doses). The length of treatment and the choice of medications depend on drug susceptibility results, the patient’s response to treatment, and the presence or absence of cavitation on the initial chest x-ray. Details on individual medications and descriptions of various treatment regimens are provided in the CDC/ATS/IDSA statement.

Isoniazid may cause a condition of the nerves that results in numbness and tingling sensations, especially in people with poor nutrition. This side effect may be avoided by administering pyridoxine (vitamin B6) along with the INH in select patients. Vitamin B6 also should be given to pregnant women who receive INH. Side effects of PZA may include liver toxicity (drug-induced hepatitis), gastrointestinal intolerance, and increased levels of uric acid (which can cause gout). Ethambutol or EMB (Myambuto™) can cause inflammation of the optic nerve, causing decreased visual acuity and impaired red/green color discrimination. Monthly monitoring of patients receiving EMB should include questions about vision and eye tests of acuity and of color vision. Streptomycin is given by injection; major side effects include toxicity to the kidneys and impaired hearing. Pyrazinamide and streptomycin should not be given to pregnant women.

In patients with pulmonary tuberculosis, sputum cultures should be monitored at least monthly following the start of therapy. Patients who have a cavity on the initial chest x-ray and fail to convert their sputum culture to negative by the end of 2 months of 4 drug therapy have a high rate of relapse; in these patients, drug susceptibility studies should be monitored and
Physicians base the combination of drugs and the length of therapy on many factors, and the complexities of case management of patients with active TB should be undertaken with close collaboration among direct care providers, the laboratory, and the local public health authority. In complex cases, such as cases involving young children or patients with HIV infection, care may be best provided with close consultation with a tuberculosis specialist.

Adherence to Therapy

In its recent statement on the Treatment of Tuberculosis, the CDC/ATS/IDSA assigned responsibility for the successful completion of treatment for tuberculosis to the provider and the public health system and not to the patient. Successful treatment of tuberculosis today requires more than the prescription of medications; the medications must be taken as prescribed, for the appropriate duration, as dictated by each individual case. Treatment for tuberculosis is lengthy, even though symptoms may disappear shortly after therapy is initiated. Patients who feel better are more likely to stop taking their medications, especially when there are other personal priorities. Problems with adherence can lead to treatment failure or relapse, with renewed spread of infection and development of drug resistance. Adherence can be encouraged by a system of patient-centered case management. The responsibility for successful completion of treatment is assigned to a specific provider, usually a nurse or a TB field worker, who is able to tailor the medication regimen as much as possible to the patient’s lifestyle. Direct observation of treatment (DOT) by a health care provider is a valuable tool in case management and should be considered the standard-of-care for all newly-diagnosed cases and TB suspects. If all attempts to achieve adherence fail, many jurisdictions provide for involuntary hospitalization under public health law to continue treatment and assure its completion. Fortunately, this measure rarely is required.

When adherence is no longer a concern, clinicians can give a one-month supply of medication at a time. Each person should receive detailed instructions about the symptoms of toxicity, as well as instructions to discontinue therapy and consult with the supervising physician immediately if side effects are suspected. A provider should see the patient at least once a month to assess for adherence, for the response to treatment, and for side effects. The vicissitudes of survival on the streets can make adherence to a rigid schedule difficult for many homeless persons. No place may be available to safely store the medications. Adherence can be enormously improved by offering DOT intermittently (e.g. 2-3 times per week) at a site frequented by the patient. Incentives or enablers (such as public transportation passes, food coupons, etc.) also may help encourage adherence. Combination medications (e.g. Rifamate™, containing INH + RIF, or Rifater™, containing INH + RIF + PZA) minimize the risk of incorrect dosing of medications. Rifater™ can be used only in daily regimens. Each dose should be documented to reduce possible confusion about adherence over a long course of therapy.

Control of Tuberculosis

General control measures

One of the best measures for controlling the spread of TB (or any infectious disease that is spread by the respiratory route via aerosol) is simple: shelter guests and staff should cover their mouths and noses when they cough or sneeze. Guests can comply with this measure more readily when tissues are easily available.

Another way to reduce the incidence of airborne infections is to provide good ventilation to outside air in all rooms. For smaller shelters this may involve opening windows. Measures such as High Efficiency Particulate Air (HEPA) filters and ultraviolet irradiation of re-circulated and upper room air have been used in an attempt to minimize spread of TB in shelters and in other long-term living spaces. However, the clinical utility of these measures is not yet clear, and we are awaiting the results of studies currently underway.

Some shelters try to assign the same bed to their guests each night. A “bed list” is kept to facilitate contact investigation in the event that an infectious case is found. In addition to promoting a sense of stability, this is excellent public health practice; the fewer persons exposed to an undiagnosed person with active pulmonary tuberculosis, the lower the number of guests at-risk for infection.

Surveillance for tuberculosis can facilitate early case finding. Educating shelter staff and guests about TB and encouraging them to report persons with an unusual or prolonged cough can lead to a diagnosis of TB in an individual with unsuspected TB disease. Criteria for medical evaluation may be based on a “cough log” that records the names of persons who are coughing at night. Shelter staff who have close
Tuberculosis (TB) is a disease caused by bacteria. The TB organism infects people through the lungs. A person ill with TB can infect others by coughing or sneezing droplets containing live TB germs into the air. However, in most circumstances TB is not highly infectious.

Contact Investigation

When a guest in a shelter has been diagnosed with active tuberculosis, the local health department usually carries out an investigation to identify and test contacts to the case. Infected contacts to an active case are among the highest risk groups for development of active disease (see above). The “contact investigation” usually is based on PPD skin testing and chest radiography of high-risk close contacts. A PPD is placed immediately, and if negative, the PPD is repeated again 8-12 weeks following the last exposure to the person with TB. QuantiFERON has not been studied adequately yet in contacts, although a positive QFT test has the same significance as a positive (5mm) PPD skin test in this setting. Infected contacts should receive treatment with INH or RIF to prevent disease.

Close contacts may include:

- friends;
- family members or co-workers who have spent hours sharing airspace with the TB patient;
- people who have slept next to the patient during the infectious period.

Shelter bed lists may help identify those sleeping next to the TB patient. If investigators find that many close contacts are infected, the circle may have to be widened, and persons less closely associated with the patient also may need an evaluation.

Molecular epidemiologic tools, such as RFLP (called “DNA fingerprinting”), can identify individual strains of TB organisms in a given case. Linked with conventional epidemiological investigations, these methods are being used by public health authorities to track transmission of tuberculosis in communities and are able to distinguish the transmission of a single strain from reactivation disease.

Summary

Tuberculosis (TB) is a disease caused by bacteria. The TB organism infects people through the lungs. A person ill with TB can infect others by coughing or sneezing droplets containing live TB germs into the air. However, in most circumstances TB is not highly infectious.

Once the droplets are breathed into the lungs, the TB bacteria multiply slowly. After a few weeks, the TB organisms spread through the body, and the immune system gradually develops a response to stop the spread over the ensuing 4-12 weeks. During this time, the person may or may not feel sick but cannot spread TB to anyone else. TB organisms that remain viable are contained in a “latent”, or dormant, state by the now-sensitized immune system.

The infection may become active in later life and lead to tuberculosis disease. The PPD skin test or the QuantiFERON (QFT) test helps identify people who have latent TB infection (LTBI), allowing caregivers to treat them with medicine to kill the bacteria before their infection becomes active. Because TB usually spreads to others when the infection becomes active, early identification and treatment of LTBI prevents the spread of TB in the community.

A person who tests PPD or QFT positive should undergo a medical evaluation, including a history, a physical examination, and a chest radiograph. If the evaluation reveals no signs of illness, medication can prevent the development of disease. Daily doses of a single anti-TB drug are used to treat LTBI: isoniazid (INH) for 9 months or rifampin (RIF) for four months, with monitoring at least monthly.

People with active TB disease usually have varied signs and symptoms of illness, although rarely some persons can be without symptoms. Cough with or without sputum, fevers, weight loss, sweats at night, swollen lymph glands, and general tiredness can be symptoms of TB. These are non-specific, and many other systemic illnesses may show these same signs or symptoms. If TB is suspected in a shelter staff person or guest, prompt evaluation by a clinician, including a chest x-ray, should be performed. Treatment of active TB requires multiple drug therapy (usually 2 to 4 medications) taken for 6 to 12 or more months.

Anti-TB drugs work well to cure TB when taken according to directions. Patient centered case management, using direct observation (and recording) of treatment doses by a health care worker (called DOT) is the standard of care. Therapy can be tailored to the patient’s lifestyle and priorities in order to maximize adherence and assure successful completion of therapy. When all attempts to achieve adherence fail, many jurisdictions impose legal measures to hospitalize the patient involuntarily to continue treatment.

All anti-TB drugs can have side effects, such as
nausea, vomiting, fevers, or skin rashes. The most serious side effects of some of the medicines (e.g. INH, RIF, PZA) involve the liver. Signs of jaundice (yellow eyes or skin, tea-colored urine) or discomfort over the liver (right upper quadrant of the abdomen) are reasons to stop the drugs immediately and refer the patient to a TB specialist.

Diagnosis of a case of active and potentially infectious TB should lead to a contact investigation to identify and treat infected close contacts of the TB patient. The local board of health usually conducts or provides assistance with these activities. ■

### Tuberculosis Medication List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Abbreviation</th>
<th>Brand Name</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>INH</td>
<td>INH</td>
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<tr>
<td>rifampin</td>
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<td>Rimactane, Rifadin</td>
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<td>EMB</td>
<td>Myambutol</td>
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<tr>
<td>streptomycin</td>
<td>SM</td>
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</tr>
</tbody>
</table>

**Combination Pills**

| INH + RIF | Rifamate | $$$ |
| INH + RIF + PZA | Rifater | $$$$ |

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