Tuberculosis and Other Mycobacterial Diseases

David Ashkin, MD, FCCP

Objectives:

1. To become familiar with the epidemiology of tuberculosis.
2. To review the pathogenesis and clinical presentation of tuberculosis.
3. To address issues concerning the prevention of tuberculosis, including the diagnosis and treatment of tuberculosis infection.
4. To review issues concerning the diagnosis and treatment of tuberculosis disease.
5. To outline pertinent topics in of Mycobacterium other than tuberculosis (*eg, M avium complex and Mycobacterium kansasii*).

Key words: multidrug-resistant TB; nontuberculous Mycobacterium; tuberculosis

Tuberculosis

Epidemiology

At the turn of the 20th century, tuberculosis (TB) was one of the leading causes of death in the United States. After the discovery of effective chemotherapy, the rate of TB significantly declined an average of 8% per year between 1953 and 1983. From 1985 to 1992, however, TB unexpectedly increased by approximately 20%. Factors associated with the resurgence included the HIV epidemic, increased immigration of foreign-born persons from high-incidence areas, an increased number of medically underserved persons (*eg,* homeless individuals, drug abusers), and probably most importantly, the deterioration of the public health infrastructure for the control of TB. Associated with the increased incidence was an increased number of drug-resistant TB cases.

With improvements in TB control, the overall number of cases in the United States has decreased over the last 8 years, but TB remains a significant national public health problem. In 2001, there were a total of 15,991 cases of TB in the nation, with a rate of 5.6 per 100,000 population (the lowest rate and total number of TB cases ever documented since national reporting began in the United States). The highest numbers of cases are reported in California, Florida, Illinois, New York, and Texas, which collectively account for 52% of TB cases nationally. It is estimated that approximately 15 million people are infected with TB in the United States, making for a large potential reservoir of disease in the population. The infection rate among foreign-born individuals in the United States is approximately seven times higher than for the US-born population. While the number of cases in the United States has recently been decreasing, the proportion of cases in the foreign-born population has increased from 27% in 1992 to 46% in 2000. In addition, 71% of the reported multidrug-resistant cases in the United States occurred in foreign-born individuals.

Worldwide, TB has not declined as in the United States. According to the most recent statistics from the World Health Organization, the number of new disease cases of TB in 2000 was approximately 8.4 million worldwide, added to the existing 16.2 million cases. Ninety-five percent of TB cases occur in developing countries (especially in Africa and Asia) where HIV infection is common and resources are scarce and unavailable to ensure proper TB treatment. It is estimated that 1.87 million people died of the disease, with a fatality rate as high as 50% in some countries with high rates of HIV coinfection. In addition, approximately one third of the world, or 1.86 billion people, are infected with *Mycobacterium tuberculosis* (MTB). To make matters worse, the incidence of drug-resistant TB worldwide is increasing. During the 1990s, an estimated 30 million people died as a result of TB, making a strong argument for its being the most important pathogen in the world today.

Causative Agent of TB

TB is caused by a group of five closely related mycobacteria *(M tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti, and Mycobacterium canettii)* which form the *M tuberculosis* complex. The MTB organism is responsible for the majority of cases of TB in the United States.

Transmission of MTB

Risk factors for acquiring TB infection, a prerequisite for the development of disease, are related to having contact with a source case. In the United States, important risk factors for infection are: close contact to a TB case; immigration from an endemic area (*eg,* Africa, Asia, or Latin America); exposure to untreated TB cases in congregate living facilities (*eg,* homeless shelters, correctional facilities, nursing homes, or other health-care facilities); age; and residence in high-incidence locations (*eg,* inner cities, travel to foreign endemic areas).

TB is usually spread from human to human, through the air by droplet nuclei, particles 1 to 5 μm in diameter containing *M tuberculosis* complex organisms. MTB enters the air when patients with active pulmonary TB cough, speak, sneeze, or sing, although coughing remains the most effective method of aerosolization. Droplet nuclei may also be produced by aerosol treatments, sputum induction, aerosolization during bronchoscopy, manipulation of lesions, or processing of tissue or secretions in the hospital or laboratory. These droplet nuclei are so small that air currents normally present in an indoor environment can keep them airborne for long periods. Individuals who are in prolonged, close contact with patients with active TB, especially in environments with poor ventilation, are most likely to inhale the organism and become infected (especially in congregate settings such as jails, prisons, shelters, hospitals, *etc*); however, only approximately one third of these exposed individuals become infected. In countries where TB is endemic, the chances of being exposed to an active case is more likely, thus increasing the chances for transmission.

When a person inhales a droplet nucleus, which may contain between 1 and 400 organisms, it usually is trapped in the upper respiratory tract and cleared. Organisms deposited on intact mucosa or skin do not invade tissue. The smallest droplets, those measuring < 5 μm, make it to the alveoli.

The chances of transmission of MTB are influenced by the following four factors: (1) the number of organisms entering the air; (2) the concentration of organisms in the air, determined by the size of the space and the adequacy of ventilation; (3) the length of time an exposed person breathes the contaminated air; and (4) possibly the immune status of the exposed individual. Some believe that HIV-infected persons and others with impaired cell-mediated immunity may be more likely to become infected with MTB after exposure than persons with normal immunity; however, those with impaired cell-mediated immunity are more likely to develop disease if they are infected (discussed later).

Pathogenesis

After inhalation, the droplet nucleus is carried down the bronchial tree to a respiratory bronchiole or alveolus, where it is phagocytized by resident alveolar macrophages. The nuclei are able to survive at this primary site of infection; bacilli multiply initially within the macrophage and within 2 weeks are transported through the lymphatics to establish secondary sites. The development of an immune response, heralded by the development of delayed-type hypersensitivity over the next 4 weeks, leads to granuloma formation with a subsequent decrease in bacillary numbers. This stage of disease is called latent TB infection (LTBI), detected by a reaction to the tuberculin skin test. Patients with TB infection are asymptomatic, but they have the potential to progress to active disease later. For most individuals with normal immune function, proliferation of MTB is arrested once cell-mediated immunity develops, though small numbers of viable bacilli may remain within the granuloma. Although a primary complex can sometimes be seen on chest radiograph, the majority of pulmonary TB infections are clinically and radiographically inapparent. Most commonly, a positive tuberculin skin test result is the only indication that infection has taken place. Individuals with LTBI but not active disease are not infectious and thus cannot transmit the organism.

Once infected with TB, 3 to 5% of "immunocompetent" individuals develop active disease within 2 years (defined as progressive primary TB, seen more commonly in patients with a large inoculation or immunosuppression) and an additional 3 to 5% develop TB during the remainder of their lifetime. Most infected individuals are able to mount an effective immune response that encapsulates these organisms, usually for the rest of the host's life, thus preventing the progression from infection to disease. Years after the initial infection and in a small proportion of patients (approximately 5%), the immune system may not be able to contain these latent organisms, so "reactivation" of TB disease

develops. Most cases of TB were thought to be due to reactivation from remote infection (about 90% of cases), but studies utilizing DNA fingerprinting indicate that recent transmission (especially among HIV-positive individuals) probably accounts for as much as 40% of cases of TB.

Some individuals appear to be more susceptible than others to progression to disease. This is particularly apparent among individuals with certain medical conditions associated with varying degrees of immunosuppression (*ie,* HIV, diabetes mellitus, certain cancers, chemotherapy or immunosuppressive therapy, silicosis, gastrectomy, old age, malnutrition, IV drug use, renal insufficiency) and in children < 4 years old. Most of these individuals have conditions that are felt to impair their cellular immunity. In fact, patients infected with HIV, with their severe defect in cellular immunity, are significantly more likely to progress from infection to disease (relative risk increased 80- to 170-fold compared to individuals not infected with HIV). Unlike immunocompetent individuals who have a 5 to 10% chance of progressing from infection to disease during their lifetimes, HIV-infected individuals coinfected with TB have a rate that may be as high as 8% per year. The risk of TB disease among HIV-infected anergic patients may be elevated.

The "partnership" between HIV and TB has augmented the deadly potentials of each disease. By destroying the CD4 cells of the host's immune system, HIV allows dormant TB to activate and rapidly cause disease. In response to the reactivation of TB, CD4 cells become stimulated and begin to replicate. This activation further renders the CD4 cells vulnerable to invasion by HIV and allows the virus to further replicate within these cells. This leads to a vicious cycle of increasing viral load, which causes a further deterioration of the host's immune system. Studies have shown that the 1-year mortality rate for treated, HIV-related TB ranges from 20 to 35% with little variation between cohorts from industrialized and developing countries.

In a person with intact cell-mediated immunity who has previously been infected with MTB, some protection against reinfection usually is present if MTB exposure recurs. In an otherwise healthy, previously infected person, any organisms that are deposited in the alveoli after reexposure are likely to be killed by the cell-mediated immune response. Exceptions may occur, but in immunocompetent individuals, clinical and laboratory evidence indicates that disease produced by the inhalation of a second infecting strain is uncommon. However, reinfection has been documented both in persons without recognized immune compromise and in those with advanced HIV infection.

Classification of TB

Table 1 outlines a classification system used mainly as an operational framework for public health programs, but which may be helpful for practicing clinicians in categorizing their patients. This classification is based on the broad host-parasite relationships as described by exposure history, infection, and disease.

Diagnosis and Treatment of Latent TB Infection

The tuberculin skin test is the most common method for identifying MTB infection in persons who do not have TB disease. Although the available tuberculin skin test antigens are substantially < 100% sensitive and specific for detection of infection with MTB, no diagnostic methods have yet proven more effective.

The tuberculin test is based on the fact that infection with MTB produces a delayed-type hypersensitivity reaction to certain antigens that are derived in extracts of culture filtrate called *tuberculin;* the preparation used for testing is called tuberculin purified protein derivative (PPD). Diagnosis of TB infection relies on determining the size of the delayed-type hypersensitivity reaction to an intradermal injection of 0.1 mL of 5TU PPD (Mantoux method). Tests should be read between 48 and 72 h after injection when the induration is maximum, although induration may last for up to 7 days. (Erythema should not be read.) The diameter of the induration, measured transversely to the long axis of the arm, should be measured

Table 1 — *Classification of Tuberculosis*

Classification	Description
0	No tuberculosis exposure, not infected
1	Tuberculosis exposure, no evidence of infection
2	Tuberculosis infection, no disease
3	Tuberculosis, clinically active
4	Tuberculosis, not clinically active
5	Tuberculosis suspected (diagnosis pending)

using a ballpoint pen. Results should be recorded as millimeters of induration. Multiple puncture tests (*eg,* tine test) are not recommended due to their low reliability.

Because of the low specificity of the tuberculin skin test in populations with a low risk of TB infection (especially in areas with an increased prevalence of nontuberculous mycobacteria), specific cutpoints have been developed to improve the specificity according to the individual's risk of true TB infection and risk of developing active disease if infected.

Induration measurement of 5 mm is considered indicative of TB infection in patients with a high probability of infection or a high risk of disease when infection is present (recent close contacts with TB patients; individuals with radiographic evidence of old TB; individuals with HIV infection, patients with organ transplants; and other immunosuppressed patients receiving the equivalent of ≥ 15 mg prednisone daily for longer than 1 month). HIV-infected persons may have a compromised ability to react to tuberculin skin tests because of cutaneous anergy associated with progressive HIV immunosuppression; however, the usefulness of anergy testing to determine any lack of delayed-type hypersensitivity response in HIV-infected persons has not been shown to be correlated and is not recommended.

Induration measuring 10 mm is considered a positive result for individuals with a moderate to high probability of TB infection (*eg*, recent arrivals [< 5 years] from endemic areas; residents and employees of high-risk congregate settings; mycobacterial laboratory personnel) or medical conditions that increase the likelihood of disease progression (Table 2).

Table 2 — *Medical Conditions That Increase Risk of Progression of TB Infection*

Injection drug use
Silicosis
Diabetes mellitus
Chronic renal failure
Lymphomas, leukemias
Cancers of head, neck, and lung
Malnutrition (weight loss >10% below ideal body weight)
Gastrectomy or jejunoileal bypass
Children younger than 4 yr who are exposed to persons at high risk for TB

Patients who do not fall into these categories should be judged to have a positive reaction with 15 mm of induration. In general, these individuals should not undergo tuberculin testing unless otherwise indicated.

Persons with "negative" tuberculin skin test reactions who are to undergo repeat annual or semiannual skin testing (*eg,* health-care workers or residents of long-term care facilities) should receive an initial two-step test to decrease the possibility of a "booster reaction" being confused with the true skin test conversion. Those patients with an initial two-step test "negative" reaction who have an increase in reaction size of ≥ 10 mm on subsequent tests should be considered to have skin test conversion indicative of recent infection with MTB.

Identification of persons with LTBI has previously been accomplished by screening individuals or groups at variable risk for TB, *ie,* widespread programs of tuberculin skin testing. In many situations, this screening was done with limited consideration of the risk of TB in the population(s) being tested. Emphasis is now on testing only those individuals at high risk who would benefit from treatment. To focus on groups at the highest risk of TB, the term *targeted tuberculin testing* is now being used. The dictum now is: the decision to perform a tuberculin test is the decision to treat (and complete). Tuberculin tests, for the most part, should not be performed in individuals for whom treatment is not contemplated. Risk of TB that is substantially greater than that in the general US population is found in persons recently infected with MTB and those with clinical conditions associated with an increased risk of progression of LTBI to active TB (Table 2). Targeted tuberculin testing should be offered only to those groups at risk and should be discouraged in individuals at low risk. Infected persons who are considered to be at high risk for developing active TB should be offered treatment for LTBI irrespective of age.

The use of terms *preventive therapy* and *chemoprophylaxis* has been confusing at times. To describe the intended intervention more accurately, the new guidelines recommend substituting the term *treatment of LTBI*. It is hoped that the change in nomenclature will promote greater understanding of the concept, resulting in more widespread implementation of this important TB control strategy.

The new guideline recommends isoniazid (INH) for 9 months (either 5 mg/kg/d, to a maximum of 300 mg, or 15 mg/kg biweekly to a maximum of 900 mg) for all individuals, instead of the previous recommendation of 6 months for adults and 12 months for those infected with HIV. This change is based on studies that revealed 9 months to be superior to 6 months, but as effective as 12 months, in preventing the development of active disease in those infected with TB. If 9 months of INH therapy cannot be accomplished, 6 months is a less efficacious alternative. Nine months of INH therapy is recommended for children. Following concerns about decreased rates of completion of preventive therapy, studies have shown that rifampin (10 mg/kg to a maximum of 600 mg) for 4 months, or rifampin (or rifabutin) with pyrazinamide (PZA) daily for 2 months in HIV-positive individuals is an effective alternative to INH. See below for precautions when utilizing this regimen. (Biweekly administration of rifampin/PZA by directly observed preventive therapy is an option if other regimens cannot be employed).

Before beginning therapy for LTBI, active disease should be ruled out. Baseline laboratory testing is not routinely indicated for all patients at the start of INH therapy or during therapy. It is recommended that all patients being treated for LTBI with INH receive an initial clinical evaluation and, at least, monthly follow-up evaluations. HIV-infected persons, pregnant women and those in the immediate postpartum period (within 3 months of delivery), persons with a history of chronic liver disease, those who use alcohol regularly, and those at risk of liver disease (*eg*, individuals taking other medications that affect liver function) should receive baseline laboratory testing. Those with abnormal baseline liver studies may require continued monitoring. All patients should be educated about the symptoms of hepatitis and be instructed to immediately notify the health-care provider if symptoms develop, at which time the medications should be immediately stopped and transaminase studies drawn. If the results are elevated fivefold above the upper limit of normal, or threefold above the upper limit of normal with symptoms present, treatment for LTBI should be withheld.

As a result of reports concerning the development of severe liver injury associated with the use of rifampin/PZA among HIV-negative individuals being treated for LTBI, the Centers for Disease Control (CDC) and the American Thoracic Society (ATS) issued revised recommendations that emphasize the need for patient counseling and enhanced symptomatic and hepatic monitoring when this regimen is used. It is recommended that routine transaminase measurements be performed at baseline, 2, 4, and 6 weeks of treatment and that therapy immediately be discontinued if symptoms develop or transaminase levels exceed fivefold normal. In addition, it is recommended that the 9-month INH regimen be used when feasible and the rifampin/PZA regimen be limited to high-risk individuals who are unlikely to complete a 9-month regimen. The rifampin/PZA regimen remains an option but should be used with caution, especially in those with a history of liver injury or alcoholism, or those who are taking medications associated with liver injury.

Clinical Manifestations, Diagnosis, and Treatment of Active TB Disease

Active TB remains primarily a disease of the pulmonary system; however, in HIV-infected individuals, up to 60% of patients with TB will have extrapulmonary involvement alone (approximately 30%) or in addition to pulmonary disease (about 33%), as opposed to 15% in individuals not infected with HIV. TB can occur in almost any organ, but the most common sites of extrapulmonary involvement include the pleura, lymph nodes (particularly cervical and hilar), the CNS (as meningitis or tuberculoma), genitourinary system, blood, and bone marrow.

The key element to the diagnosis of TB is to have a high degree of suspicion, especially in those groups at high risk. Early recognition of the disease is essential to stop further transmission, but no single clinical, radiographic, or laboratory tool is sensitive or specific enough to be diagnostic so astute clinical assessment is required.

A careful history to elicit the most common symptoms of pulmonary TB (*ie,* fever, productive cough, weight loss, wasting, night sweats, shortness of breath, and occasionally hemoptysis) should be obtained. The systemic nature of many of these symptoms is due to the cytokine release associated with the inflammatory response by the host to the organism. These symptoms are usually present for a prolonged period, characteristically weeks to months. A history of possible TB exposure risk (*eg,* previous exposure, history of homelessness or

prolonged stay in a correctional or other congregate setting, drug abuse history, migration from an endemic area, prior PPD test) should also be elicited. Physical examination generally is not helpful in establishing the diagnosis.

Patients with prolonged symptoms, especially those at high risk for TB, should undergo a chest radiograph immediately (Table 3). Pulmonary TB in immunocompetent hosts nearly always causes abnormalities on the chest film, although an endobronchial lesion may not be associated with a radiographic finding. In primary TB occurring as a result of recent infection, the process is generally seen as a middle or lower lung zone infiltrate, often associated with ipsilateral hilar adenopathy. In primary pulmonary pleuritis, a unilateral pleural effusion may be present. The PPD results initially may be negative in these cases. Pleural fluid findings are usually predominated by lymphocytes, negative for acid-fast bacilli (AFB) and positive on culture in only 50 to 60% of cases. The addition of pleural biopsy for histologic studies and culture increases the yield to approximately 80%.

Pulmonary TB that develops as a result of endogenous reactivation of latent infection in immunocompetent hosts usually causes abnormalities in the upper lobes of one or both lungs. Cavitation is common in this form of TB. The most frequent sites are the apical and posterior segments of the lung, with the right lung affected slightly more often than the left. Healing of the tuberculous lesions usually results in a scar, with loss of lung parenchymal volume and often calcification. In the immunocompetent adult with TB, intrathoracic adenopathy is uncommon but may occur, especially with primary infection. As TB progresses, infected material may be spread via the airways into other parts of the lungs, causing a patchy bronchopneumonia. Erosion of a parenchymal focus of TB into a blood or lymph vessel may lead to dissemination of the organism and a miliary pattern (evenly distributed small nodules) on the chest film.

Table 3 — *General Indications for Chest Radiograph To Detect TB**

Unexplained cough (>3 wk)
Unexplained cough with fever (>3 d)
Unexplained pleuritic chest pain, hemoptysis, and/or dyspnea
Unexplained fever, night sweats, weight loss

*From Pitchenik AE, Brooks R. The most common clinical mistakes in prevention, diagnosis and therapy of tuberculosis. In: Tuberculosis in Florida: the clinician's desktop reference. Florida TB Control Coalition, 1999.

Nodules and fibrotic scars are seen most commonly in "old healed" TB and may contain slowly multiplying tubercle bacilli with the potential for future progression to active TB. The risk of progression is significant, and persons who have nodular or fibrotic lesions consistent with findings of previous disease on chest radiograph, and who have a positive tuberculin skin test reaction, should be considered high-priority candidates for treatment of latent infection, regardless of age.

In patients with HIV infection, the nature of the radiographic findings depends to a certain extent on the degree of immunosuppression. TB that occurs relatively early in the course of HIV infection tends to have the typical radiographic findings described earlier. With more advanced HIV disease, the radiographic findings become more atypical; cavitation is uncommon, and lower lung zone or diffuse infiltrates and intrathoracic adenopathy are frequent. Clear lung fields may be present in up to 35% of patients with active TB and AIDS.

Patients with symptoms or chest radiographic findings suspicious for TB disease should be immediately isolated if they are admitted to a health-care facility or congregate setting.

The foundation of rapid, accurate microbiological diagnosis of TB is proper specimen collection and rapid transport to the laboratory. At least three sputum specimens should be sent for AFB smear, culture, and (in some cases) nucleic acid amplification, to attempt to establish the diagnosis microbiologically. A quality sputum specimen should contain a volume of 5 to 10 mL. If the patient is unable to produce an adequate specimen, sputum induction and/or bronchoscopy should be considered (with proper infection control precautions used).

Sputum smears, the time-honored test for the diagnosis of TB, are only positive in approximately 50% of active cases. The advantage of the smear is that it is both rapid and cheap. The reason for its low sensitivity is the need for 10,000 to 100,000 organisms in a milliliter of specimen. In addition, the smear is not specific, as other mycobacteria also may have a similar appearance. Patients with smear-positive sputa are more likely to transmit infection to contacts compared to those with smear-negative studies, although this latter group has clearly been shown to transmit infection.

Culture results are positive in approximately 80% of cases, but unfortunately take a prolonged

time to grow: up to 8 weeks for solid media and 1 to 3 weeks for liquid media. A positive culture requires a result of at least 500 organisms per milliliter. Susceptibility testing (which should be performed on all initial isolates) may take another 1 to 3 weeks.

Fifteen to twenty percent of diagnosed cases cannot be confirmed microbiologically and are considered to be culture-negative or clinical TB. In these patients, the diagnosis is based on the presence of symptoms, positive tuberculin skin test, a radiographic appearance compatible with TB, and an improvement in clinical status after treatment with antituberculous therapy, despite negative microbiological studies and no other etiology accounting for the illness. This is found more often in children and individuals from whom quality specimens are difficult to obtain. Bronchoscopic studies using BAL and transbronchial biopsy, done with appropriate infection control precautions, may help establish the diagnosis and rule out other etiologies when the diagnosis is in question. When TB is strongly suspected, initiation of presumptive antituberculous therapy is appropriate while awaiting microbiological confirmation.

Nucleic acid amplification techniques hold the promise of being able to detect a few strands of nucleic acid in a sample, amplify it, and identify the presence of TB within a matter of hours. The test is > 90% sensitive and 99% specific when used in smear-positive cases. Unfortunately, in smear-negative cases, the sensitivity may only be 60 to 80%. The test has been approved by the US Food and Drug Administration for use on respiratory specimens (not approved for nonrespiratory specimens) from untreated cases. Most authorities recommend using multiple specimens to improve the test sensitivity; however, the clinician must be aware that a negative test does not rule out the possibility of TB and that a positive test might not guarantee a diagnosis of TB.

Since the advent and utilization of effective chemotherapy against TB in the 1950s, 95% of all individuals with pansusceptible TB who complete therapy are now cured. In those individuals with multidrug-resistant strains (resistant to at least INH and rifampin), over 40% of cases may fail to respond to traditional chemotherapy.

The ATS and the CDC recommended that four-drug therapy with INH, rifampin, PZA, and either ethambutol or streptomycin be started initially in patients from areas where INH resistance exceeds 4%, until susceptibility test results are available. In areas with < 4% INH resistance, the fourth drug may be omitted from the initial regimen. Once the results reveal susceptibility to INH, rifampin, and PZA, the ethambutol or streptomycin should be discontinued. After 2 months of therapy, PZA is stopped, and INH and rifampin are continued for an additional 4 months for a total of 6 months of treatment. If cultures are not negative after 2 months of therapy, then treatment should be extended for at least 4 months after negative results are achieved. This regimen can be given effectively either daily or intermittently, utilizing directly observed therapy (DOT) [Table 4]. It may also be used for those individuals infected with HIV, as well as patients with extrapulmonary disease (except for children with miliary TB, bone/joint TB, or tuberculous meningitis, who should receive a minimum of 12 months of therapy). If PZA cannot be given for the first 2 months, a reasonable alternative is INH and rifampin administered for 9 months. A 4-month regimen of INH and rifampin is acceptable therapy for adults who have active TB and who have negative smears and cultures (culture negative or clinical TB).

It is essential to treat pregnant women who have active TB. INH and rifampin have been shown to be safe in pregnancy and should be administered. PZA, although recommended by many authorities, has not been thoroughly studied in pregnancy and

Table 4 — *TB Treatment Options for Adults and Children*

Option	Frequency	Medications
1	Daily Daily or 2-3 times weekly†	INH, rifampin, PZA, and ethambutol or streptomycin for 8 wk;* then INH and rifampin for 16 weeks
2	Daily Twice weekly	INH, rifampin, PZA, and ethambutol or streptomycin for 2 wk;* then Same as above for 6 wk, then INH and rifampin for 16 wk†
3	3x weekly†	INH, rifampin, PZA, and ethambutol or streptomycin for 24 wk*†

*Omit fourth drug in areas where INH resistance < 4%.
†Intermittent dosing should be administered via DOT.

should be used at the discretion of the treating clinician. Streptomycin has been shown to be harmful to the developing fetus and should not be used in pregnancy.

Corticosteroids have been shown to be of benefit in preventing cardiac constriction from TB pericarditis and in decreasing neurologic sequelae resulting from TB meningitis. They may have a role in preventing bronchial stenosis in cases of diffuse endobronchial TB.

The need to treat with multiple drugs for a prolonged period leads to the major obstacle facing the control of TB: adherence to therapy. If patients do not take their medications as prescribed for the entire period, treatment failure and resistance may develop. Once medications are begun, adherence needs to be assured. The recent decline of TB in the United States has been attributed in large part to the implementation and utilization of DOT, which has been shown to significantly improve the completion rates of TB therapy, as well as impede the development of resistant strains. Through DOT, representatives of health-care facilities (usually from the public health system) go into the community to observe and assure that patients take their medications. Numerous studies have demonstrated that there is no reliable way to predict which patient will be adherent to therapy; therefore, all patients with active TB disease should be considered for DOT. Those not started on DOT should be given combination pills (pills containing INH, rifampin and PZA together) to avoid monotherapy and the subsequent development of resistance.

Patients must be monitored for effectiveness of treatment and toxicity. Soon after starting therapy, patients should experience an improvement in symptoms (such as cough, fevers, night sweats) and weight gain. Those who do not experience an symptom improvement or who fail to convert their cultures to negative within 2 months of treatment initiation should be evaluated for treatment failure. More than 90% of patients on appropriate therapy have negative culture results after 2 months of treatment.

Potential reasons for treatment failure include: (1) resistance to prescribed medications or the use of an inadequate combination of drugs, resulting in increased drug resistance; (2) inadequate medication levels caused by malabsorption, food or drug interactions, or concurrent medical conditions; and (3) noncompliance with prescribed treatment regimens. Of these, the latter is by far the most common cause of treatment failure. It is important to seek the advice of a TB expert when patients have resistant disease, a complicating concurrent medical conditions, or lack of expected response to therapy.

Adverse reactions are not uncommon in the treatment of TB. INH, best known for its hepatotoxicity, also causes peripheral neuropathy for which vitamin B_6 (pyridoxine) is prescribed as prophylaxis. Rifampin may cause hepatotoxicity in addition to muscle and joint stiffness and pain. Baseline liver function tests should be performed for all patients beginning treatment, and monthly monitoring is recommended for anyone with baseline abnormalities or concomitant liver disease. Clinical monitoring, by eliciting symptoms of toxicity, is recommended for all other patients. If transaminase levels become elevated and symptoms of hepatitis occur, all medications should be discontinued. Once signs and symptoms resolve or improve, medications should be reintroduced sequentially and the patient should be monitored for recurrence of hepatitis. PZA can also cause hepatotoxicity as well as high uric acid levels resulting in gout-like symptoms. Ethambutol is associated with optic neuritis, especially in doses > 20 mg/kg/d and in patients with renal insufficiency. Monthly assessment of visual acuity and color discrimination is recommended to identify patients who may be experiencing this toxicity.

Drug resistance has been increasing in the United States as well as worldwide. The most common reasons for the development of drug resistance are patient nonadherence and physician mistakes (*eg*, adding a single drug to a failing regimen). Multidrug-resistant TB is defined as strains resistant to at least INH and rifampin. Outbreaks of such strains have been well documented, resulting in significant morbidity and mortality, especially among HIV-infected populations. Control and prevention of such outbreaks have required the expenditure of significant efforts and resources by hospital and TB control programs. Treatment of multidrug-resistant TB is frequently unsuccessful, requiring the use of more toxic, expensive drugs, in addition to possible surgery; thus, emphasis is on prevention. In patients with suspected drug-resistant TB, treatment should be started with the recommended four drugs plus at least two additional agents to which the patient's organism is thought to be susceptible.

In patients with confirmed multidrug-resistant disease, therapy with three drugs to which the isolate is susceptible is recommended for at least 12 months after documented conversion of the cultures to negative. Most experts recommend 18 to 24 months of total therapy. Patients with INH-resistant TB can be treated with rifampin, PZA, and ethambutol for 6 to 9 months. Patients with rifampin-resistant TB should be treated with isoniazid, PZA, and ethambutol for at least 12 months after cultures convert to negative. Consultation with a TB expert is recommended for the management of drug-resistant TB.

Patients with HIV have a response to therapy similar to that of individuals without HIV infection; however, the treatment of HIV has altered TB therapy. Protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), two of the most potent agents available to control HIV, interfere with rifampin, the most important drug available in TB treatment. Rifampin is a potent inducer of the hepatic p450 system. This induction enhances the metabolism of the PIs and NNRTIs, causing reduced serum levels and leading to ineffective viral suppression, as well as the development of resistance. Conversely, the PIs and NNRTIs interfere with the metabolism of the rifamycins, causing high serum levels and potential toxicity.

Based on more recent experience, rifabutin–a rifamycin derivative with less effect on the hepatic p450 system, but equivalent efficacy against TB–may be used safely and effectively with the PIs. More experience is necessary, however, to determine the correct dosages and best regimens to utilize.

With the use of antiretroviral therapy and the subsequent improvement in the host's immune response, patients with TB disease may actually exhibit a "paradoxical" worsening of their clinical condition, thought due to an inflammatory response from the immune reactivation. These patients may experience the development of new ascites, lymphadenopathy, fever, pleural effusions or cerebral lesions. These may be life-threatening conditions, depending on the site and size of the lesion. Clinicians treating TB patients with HIV must be aware of this phenomenon and rule out other etiologies that maybe responsible for development of the lesions and / or clinical worsening. If no other etiology can be found, continued treatment for HIV and TB usually results in an improvement without further intervention. In selected cases, the use of immunomodulators (*eg*, steroids) may be indicated to slow the progression of this response.

Infection Control

Given the increased number of immunosuppressed individuals in health-care facilities, infection control efforts to stem nosocomial outbreaks of TB among patients and staff is essential. All patients suspected of having active TB should be immediately isolated and kept there until they are no longer infectious or until TB has been ruled out. Isolation rooms should have negative air pressure to prevent infected air from entering hallways and should use at least six air exchanges per hour. Health-care workers who are caring for these individuals should wear N95 masks to avoid inhaling infectious particles while working in the enclosed room. Observance of these guidelines is especially important in rooms where cough-inducing procedures are performed. Patients in health-care facilities can be removed from isolation once they have received medications for 10 to 14 days, they are responding clinically, and their AFB smears are negative. Patients may be discharged from the hospital before they are removed from respiratory isolation if: (1) they are returning to their previous residence (in noncongregate settings) and the health department has assessed that no vulnerable individuals (immunocompromised persons and children < 2 years of age) are present; and (2) others who have been exposed have been evaluated for preventive therapy.

Vaccination

Bacillus of Calmette-Guérin (BCG), an attenuated strain of *M bovis*, was first used as a vaccine in humans in the early 1920s. It has since become the most widely used vaccine preparation in the world, despite questions regarding its 0 to 80% efficacy in preventing pulmonary TB in adults. Although the data are less than ideal, numerous studies have consistently shown the effectiveness of BCG in reducing the incidence of TB in infants and young children, particularly against potentially fatal disseminated TB. For this reason, BCG remains an important part of vaccine programs because of the effectiveness in reducing pediatric mortality rates for disseminated TB. Its inferior efficacy in preventing TB, compared to INH treatment for latent

infection, and the interference with tuberculin skin testing has limited it use in the United States.

Diagnosis and Treatment of Pulmonary Disease Caused by Nontuberculous Mycobacteria

Epidemiology, Transmission, and Pathogenesis

Although not as important worldwide as TB, diseases due to other mycobacteria appear to be more common than TB in the United States. The recognition of these pathogens is relatively recent. These organisms, characterized as the nontuberculous mycobacterium (NTM), share a number of features. Unlike MTB, NTM are normal inhabitants of the environment (usually soil and water). Also, unlike TB, pulmonary disease and other infections caused by the NTM are not contagious, and patients with these diseases are generally not isolated. Many clinicians believe these organisms to be opportunists rather than virulent pathogens, because some local or systemic immune impairment is required for them to cause disease.

Much remains to be understood about the pathogenesis of NTM infection and disease. It is assumed most persons are infected by the environmental NTM. Aerosolization of environmental NTM may play a role in respiratory disease, whereas ingestion may be the source of infection for children with NTM lymphadenitis and for most patients with AIDS, whose disseminated *M avium* or *Mycobacterium genavense* begins as a GI colonization. Bacteremic spread of the organism in patients with AIDS then involves multiple organ systems, including bone marrow, lymph nodes, liver, and spleen. Direct inoculation with NTM organisms from water or other material is the likely source of infection in patients with soft tissue infections. It is not known whether NTM disease develops soon after infection or, like TB, develops after a period of latency.

Clinical Manifestations

Early reports concerning patients with pulmonary disease caused by NTM involved older white men with a history of underlying lung disease. The diseases appeared regional, with most patients from the rural southeastern United States having disease caused by *M avium*, while most from the central states had disease caused by *M kansasii.* NTM disease is not reportable in the United States, and an accurate incidence of the disease is limited. Severely immunosuppressed (CD4 counts < 100 cells/μL), HIV-infected individuals are particularly susceptible to disseminated disease caused by *M avium.* Before the widespread use of highly active antiretroviral therapy, HIV-infected individuals with CD4 counts <100 cells/μL developed disseminated *M avium* disease at a rate of 20% annually. Localized pulmonary disease due to *M avium* occurs in < 5% of cases in HIV-infected hosts. With the effective use of highly active antiretroviral therapy, however, the incidence of *M avium* disease seems to be declining.

Chronic pulmonary disease is the most common localized manifestation of NTM; it usually appears in older individuals, but not all patients have a history of underlying lung disease. *M avium* complex (MAC) [consisting of *M avium* and the less common, but difficult to distinguish, *Mycobacterium intracellulare*] and *M kansasii* are the most frequent NTM pathogens causing lung disease in the United States. Other less common NTM pathogens include *Mycobacterium abscessus, Mycobacterium fortuitum, Mycobacterium szulgai, Mycobacterium simiae, Mycobacterium xenopi, Mycobacterium malmoense, Mycobacterium celatum,* and *Mycobacterium asiaticum.*

Pulmonary disease caused by MAC generally falls into three syndromes:

1. Upper lobe disease that mimics reactivated TB clinically and radiographically. This is the best known syndrome. Patients are generally older men with a history of COPD.
2. MAC that develops as a complication of prior bronchiectasis. This condition is usually seen in patients with a previous history of TB or *M kansasii* who present with a recurrence of symptoms and a new infiltrate in an area of old disease. These patients also tend to be older, but there is no sexual predilection and no relationship to smoking-related disease. This syndrome also may occur in patients with bronchiectasis due to prior virus- or bacterial-related damage or cystic fibrosis.
3. MAC with no underlying disease. These patients are predominantly women, are non-smokers, and have interstitial rather than cavitary radiographic changes, which usually are confined to the lingula and right middle lobes (referred to as *Lady Windemere syndrome).* Some investigators have noted a progression to respiratory failure in some

individuals. The finding of MAC in these patients was thought to be colonization, but recent studies utilizing high-resolution CT suggest that the development of bronchiectasis in these patients is due to pathologic disease caused by MAC.

Signs and symptoms of NTM pulmonary disease are variable and nonspecific. They include chronic cough, sputum production, and fatigue. Less commonly, malaise, dyspnea, fever hemoptysis, and weight loss can occur, usually with advanced NTM disease. Evaluation is often complicated by the symptoms caused by coexisting lung diseases, including chronic obstructive airway disease associated with smoking, bronchiectasis, previous mycobacterial diseases, cystic fibrosis, and pneumoconiosis.

There are some differences in the radiographic features of NTM lung disease compared with those produced by MTB. NTM tend to cause thin-walled cavities with less surrounding parenchymal infiltrate, have less bronchogenic but more contiguous spread of disease, and produce more marked involvement of pleura over the involved areas of the lungs. Occasionally, they may produce dense pneumonic disease or a solitary pulmonary nodule without cavitation. Basal pleural disease is not often found, and pleural effusion is rare. High-resolution CT studies have shown that up to 90% of patients with mid and lower lung field noncavitary disease with MAC have associated multifocal bronchiectasis, with many patients having clusters of small (<5 mm) nodules in associated areas of the lung.

Diagnosis

In the absence of specific diagnostic features in the history, physical examination, and chest radiograph, culture isolation of the NTM is essential; however, because these organisms are commonly found in nature, contamination of culture material or transient infection does occur. Thus, a single positive sputum culture, especially with a small number of organisms, is not always sufficient to diagnose NTM disease. The previous notion that individuals had true "colonization" with NTM (*eg*, no tissue invasion) is now thought to be probably rare. Given the changing understanding of disease caused by NTM, the ATS published an official statement concerning diagnostic criteria of NTM lung disease in HIV seropositive and seronegative hosts. These criteria fit best with MAC, *M abscessus*, and *M kansasii*, as too little is known about other NTM to be certain how applicable these criteria would be.

The following criteria should be used to establish a diagnosis of pulmonary disease caused by NTM. The criteria apply to symptomatic patients with infiltrate, nodular or cavitary disease, or high-resolution CT scans that show multifocal bronchiectasis or multiple small nodules. At least three respiratory samples from each patient should be evaluated. Those having one of the following should be considered to have disease caused by NTM:

1. If results of three sputum/bronchial washes from the previous 12 mo are available, three cultures are positive with negative AFB smear results, or two cultures and one AFB smear are positive.
2. If only one bronchial wash is available, the culture is positive with a 2+, 3+, or 4+ result on AFB smear or 2+, 3+, or 4+ growth on solid media.
3. If sputum/bronchial wash evaluations are not diagnostic or another disease cannot be excluded, transbronchial or lung biopsy results reveal a NTM or mycobacterial histopathologic features (granulomatous inflammation and/or AFB) and one or more sputum or bronchial washings are positive for an NTM, even if the counts are low.

Other reasonable causes for the disease should be excluded and expert consultation should be sought when diagnostic difficulties are encountered.

Routine susceptibility testing of all NTM is discouraged, but such testing is warranted to obtain baseline data for unresponsive disease, or when relapses occur.

Treatment

M kansasii: Treatment for pulmonary disease caused by this organism was disappointing before the advent of rifampin therapy. With the introduction of rifamycins, the rate of treatment failures has decreased. The recommended treatment for adults consists of a regimen of daily isoniazid (300 mg), rifampin (600 mg), and ethambutol (25 mg/kg for 2 months, then 15 mg/kg) for 18 months, with a minimum of 12 months of treatment after culture results are negative. Clarithromycin or rifabutin

must be substituted for rifampin in HIV-positive patients who take PIs.

M avium: Medical treatment of pulmonary disease caused by MAC in HIV-negative patients historically has been frustrating and disappointing. Significant advances in the drugs available (*eg,* newer macrolides) have been made, however, and there is now greater expectation that pulmonary MAC disease can be effectively treated (defined as high rates of sputum conversion with long-term negative results on culture) with medications alone. Treatment consists of a regimen of daily clarithromycin (500 mg bid) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (300 mg), and ethambutol (25 mg/kg for 2 months, then 15 mg/kg) in adults not infected with HIV. Streptomycin two to three times weekly should be considered for the first 8 weeks as tolerated. Patients should be treated until cultures are negative for 1 year.

Disseminated MAC *Disease in HIV-Infected Patients:* Therapy in adults should include clarithromycin (500 mg bid) or azithromycin (250 to 500 mg), plus ethambutol (15 mg/kg/d). Consideration should be given to the addition of a third drug (preferably rifabutin at a dose of 300 mg/d). Therapy should be continued for life until more data become available. Prophylaxis should be given to adults with AIDS with CD4 counts < 50 cells/μL, especially in the presence of a history of prior opportunistic infections. Rifabutin (300 mg/d), clarithromycin (500 mg bid), azithromycin (1,200 mg once weekly), and azithromycin (1,200 mg once weekly) plus rifabutin 300 mg daily.

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Notes