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KEY CONCEPTS

- 1 Tuberculosis (TB) is the most prevalent communicable infectious disease on earth; it remains out of control in many developing nations. These nations require medical and financial assistance from developed nations in order to control the spread of TB globally.
- 2 In the United States, TB disproportionately affects ethnic minorities as compared with whites, reflecting greater ongoing transmission in ethnic minority communities. Additional TB surveillance and preventive treatment are required within these communities.
- 3 Coinfection with human immunodeficiency virus (HIV) and TB accelerates the progression of both diseases, thus requiring rapid diagnosis and treatment of both diseases.
- 4 Mycobacteria are slow-growing organisms; in the laboratory, they require special stains, special growth media, and long periods of incubation to isolate and identify.
- 5 TB can produce atypical signs and symptoms in infants, the elderly, and immunocompromised hosts, and it can progress rapidly in these patients.
- 6 Latent TB infection (LTBI) can lead to reactivation disease years after the primary infection occurred.
- 7 The patient suspected of having active TB disease must be isolated until the diagnosis is confirmed and the patient is no longer contagious. Often, isolation takes place in specialized “negative-pressure” hospital rooms to prevent the spread of TB.
- 8 Isoniazid and rifampin are the two most important TB drugs; organisms resistant to both these drugs (multidrug-resistant TB [MDR-TB]) are much more difficult to treat.
- 9 Never add a single drug to a failing regimen!
- 10 Directly observed treatment should be used whenever possible to reduce treatment failures and the selection of drug-resistant isolates.

1 Tuberculosis (TB) remains a leading infectious killer globally. TB is caused by *Mycobacterium tuberculosis*, which can produce either a silent, latent infection or a progressive, active disease.¹ Left untreated or improperly treated, TB causes progressive tissue destruction and,

eventually, death. Because of renewed public health efforts, TB rates in the United States continue to decline. In contrast, TB remains out of control in many developing countries—to the point that one-third of the world’s population currently is infected.¹ Approximately 1 person dies of TB in India each minute (*Times of India*, August 29, 2003). Given increasing drug resistance, it is critical that a major effort be made to control TB before the most effective drugs are lost permanently.

M. tuberculosis preferentially infects humans, and the closely related *Mycobacterium bovis* causes a similar disease in cattle and other livestock. Although uncommon today, humans frequently developed TB by drinking milk contaminated with *M. bovis*—a threat that spurred the development of pasteurization. Today, airborne *M. tuberculosis* is the main threat to humans.

Evidence of TB has been found in ancient human remains, and ancient texts describe it.^{1–3} TB commonly was known as “consumption” because of the pronounced weight loss that it caused.¹ Other common names included “wasting disease” and the “white plague.” As the term *plague* implies, TB had a profound impact on human history, most notably in Europe. (Note: The “black plague,” or bubonic plague, is a separate disease caused by *Yersinia pestis*.)

TB rates generally have risen with increasing urbanization and overcrowding because it is easier for an airborne disease to spread when people are packed closely together.³ Hence TB became a significant pathogen in Europe during the Middle Ages and peaked during the Industrial Revolution, when it caused approximately 25% of all deaths in Europe and in the United States.^{1–3} This dire threat led to the rise of public health departments and to procedures such as the isolation of infected patients. Thus TB was directly responsible for many of the healthcare practices that we take for granted today. Unfortunately, in developing nations, some of these practices are not widely available, and TB continues to rage unabated.

EPIDEMIOLOGY

Globally, roughly 2 billion people are infected by *M. tuberculosis*, and roughly 2 to 3 million people die from active TB each year despite the fact that it is curable.^{1,2,4} In the United States, about 13 million people are latently infected with *M. tuberculosis*, meaning that they are not currently sick but that they could fall ill with TB at any time. The United States had 14,093 new cases of active TB in 2005 and about 1,500 deaths.⁵ (For detailed data analysis, visit the Centers for Disease Control and Prevention [CDC] website at www.cdc.gov/nchstp/tb.) The annual incidence of TB in the United States declined by approximately 5% per year from 1953 to 1983⁶ (Fig. 116–1). In 1984, this decline slowed, and then the incidence of TB rose from 1988 to 1992, reaching 10.5 cases per 100,000 population. Since 1992, more effective infection control practices and treatment protocols have reduced TB rates to 4.8 per 100,000 population as of 2005.⁵ Despite this good news, the eradication of TB from the United States remains very

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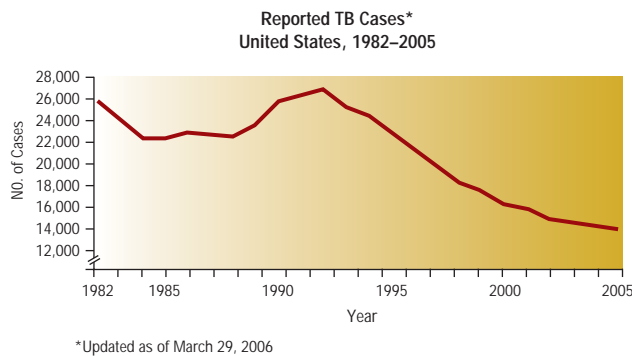


FIGURE 116-1. Reported tuberculosis cases in the United States, 1982–2003.

difficult. One reason is that we continue to import new cases from countries where TB remains out of control.^{4,5}

RISK FACTORS FOR INFECTION

Location and Place of Birth

TB can infect anyone, but the risk is not evenly distributed across the U.S. population. The major points of entry into the United States have the most TB cases. Seven states (California, Florida, Georgia, Illinois, New Jersey, New York, and Texas) reported more than 400 cases each for 2005; combined, these seven states accounted for 59.7% (8,414 cases) of the national total.⁵ Within these states, TB is most prevalent in large urban areas.⁴

The TB rate among foreign-born persons was 8.7 times that of U.S.-born persons in 2005.⁵ The percentage of foreign-born TB patients in the United States has increased annually since 1986, reaching 54% in 2005.⁵ More than half (56.0%) of the foreign-born cases in 2005 were reported in persons from Mexico (1,930), the Philippines (826), Vietnam (576), India (563), and China (389).⁵ Therefore, healthcare workers must “think TB” when caring for patients from these countries who experience symptoms such as cough, fever, and weight loss.

Close contacts of pulmonary TB patients are most likely to become infected.²⁻⁴ These include family members, coworkers, or coresidents in places such as prisons, shelters, or nursing homes. The more prolonged the contact, the greater is the risk, with infection rates as high as 30%.^{5,6} Although many circumstances exist, TB patients frequently have limited access to healthcare, live in crowded conditions, or are homeless.^{2,4} Many patients have histories of alcohol abuse or illicit drug use, and many are coinfecting with hepatitis B or human immunodeficiency virus (HIV). These concurrent social and health problems make treating some TB patients particularly difficult.

Race, Ethnicity, Age, and Gender

2 In the United States, TB disproportionately affects ethnic minorities. Hispanics, blacks, and Asians had TB rates 7.3, 8.3, and 19.6 times higher than whites in 2005.⁵ Hispanics accounted for 28.4% of all TB cases, followed by blacks at 27.9%.⁵ Asians and Pacific Islanders accounted for 22.5%, whereas non-Hispanic whites accounted for only 21.2% of the new TB cases.⁵

TB is most common among people 25 to 44 years of age (35% of all U.S. cases in 2002), followed by those 45 to 64 years of age (28%) and 65 years of age and older (21%).⁶ TB is more common in older whites and Asians compared with younger people from these groups. This reflects reactivation of latent infection acquired many years earlier when TB was very common. Older blacks and Hispanics also have more TB than younger individuals, but the differences by age are not as pronounced.⁶ This reflects a greater recent transmission among younger blacks and

Hispanics compared with younger whites and Asians. Until the age of 15 years, TB rates are similar for males and females, but after that, the male predominance increases with each decade of life.⁶

Coinfection with Human Immunodeficiency Virus (HIV)

3 HIV is the most important risk factor for active TB, especially among people 25 to 44 years of age.^{2,4,6,7} TB and HIV seem to act synergistically within patients and across populations, making each disease worse than it might otherwise be. Roughly 10% of U.S. TB patients are coinfecting with HIV, and roughly 20% of TB patients ages 25 to 44 years are coinfecting.^{5,6} HIV coinfection may not increase the risk of acquiring *M. tuberculosis* infection, but it does increase the likelihood of progression to active disease.^{1,7} Furthermore, TB and HIV patients share a number of behavioral risk factors that contribute to the high rates of coinfection.^{2,8,9}

RISK FACTORS FOR DISEASE

Once infected with *M. tuberculosis*, a person’s lifetime risk of active TB is approximately 10%.^{2,4,7} The greatest risk for active disease occurs during the first 2 years after infection. Children younger than 2 years of age and adults older than 65 years of age have two to five times greater risk for active disease compared with other age groups. Patients with underlying immune suppression (e.g., renal failure, cancer, and immunosuppressive drug treatment) have 4 to 16 times greater risk than other patients. Finally, HIV-infected patients with *M. tuberculosis* infection are 100 times more likely to develop active TB than normal hosts.^{4,10} HIV-infected patients have an annual risk of active TB of approximately 10%, rather than a lifetime risk at that rate. Therefore, all patients with HIV infection should be screened for tuberculous infection, and those known to be infected with *M. tuberculosis* should be tested for HIV infection.

ETIOLOGY

M. tuberculosis is a slender bacillus with a waxy outer layer.^{2,7} It is 1 to 4 microns in length, and under the microscope, it is either straight or slightly curved in shape.^{1,11,12} It does not stain well with Gram stain, so the Ziehl-Neelsen stain or the fluorochrome stain must be used instead.^{1,2,7} After Ziehl-Neelsen staining with carbol-fuchsin, mycobacteria retain the red color despite acid-alcohol washes. Hence they are called *acid-fast bacilli*.¹¹ After staining, microscopic examination (“smear”) detects about 8,000 to 10,000 organisms per milliliter of specimen, so a patient can be “smear negative” but still grow *M. tuberculosis* on culture. Microscopic examination also cannot determine which of the 100+ mycobacterial species is present or whether the organisms in the original samples were alive or dead.^{1,11,12} On smear, they are all dead. On culture, *M. tuberculosis* grows slowly, doubling about every 20 hours. This is very slow compared with gram-positive and gram-negative bacteria, which double about every 30 minutes.

Among the mycobacteria, only *M. tuberculosis* is a frequent human pathogen. Some nontuberculous mycobacteria such as *Mycobacterium kansasii*, *Mycobacterium fortuitum*, and *Mycobacterium avium* complex (MAC) cause infections in patients with other medical problems, especially the acquired immunodeficiency syndrome (AIDS). Chapter 129 discusses the treatment of these infections.

CULTURE AND SUSCEPTIBILITY TESTING

4 Direct susceptibility testing involves inoculating specialized media with organisms taken directly from a concentrated, smear-positive specimen.^{1,11,12} This approach produces susceptibility results in 2 to 3

weeks. Indirect susceptibility testing involves inoculating the test media with organisms obtained from a pure culture of the organisms, which can take several more weeks. The most common agar method, known as the *proportion method*, uses the ratio of colony counts on drug-containing agar to that on drug-free agar.^{1,12} In the United States, the critical proportion for resistance is 1%. That means that if a drug-containing plate shows only 2% of the growth seen on a drug-free plate, some of the organisms from the specimen were resistant to that drug. Therefore, it is likely that many of the organisms in the patient also are resistant to that drug, and it should not be used to treat that patient.

The proportion method's limitations include many weeks to obtain results, drug degradation during the incubation, and a qualitative result (susceptible or resistant). The BACTEC system (Becton-Dickinson, Sparks, MD) uses liquid medium (7H12 broth) and detects live mycobacteria based on the release of radiolabeled CO₂.¹¹ Advantages of the BACTEC system include reduced incubation time (as few as 9 to 14 days), reduced drug loss in the medium, and when multiple concentrations are tested, a truly quantitative end point (minimal inhibitory concentration [MIC]).^{1,11,12} Newer, nonradiometric rapid methods such as the MGIT system are now being used by some laboratories.¹³

Rapid-identification tests are now available.¹³ Nucleic acid probes such as the AccuProbe (Gen-Probe, San Diego, CA) use DNA probes to identify the presence of complementary rRNA (ribosomal ribonucleic acid) for several mycobacterial species.^{7,11,14} DNA fingerprinting using restriction-fragment-length polymorphism analysis has been used to identify clusters of cases.^{1,11,14} Amplification of the genetic material can be achieved through polymerase chain reaction (Roche Molecular Systems, Branchburg, NJ), the amplified *M. tuberculosis* direct (MTD) test (Gen-Probe, San Diego, CA), and strand-displacement amplification (SDA; Becton-Dickinson, Sparks, MD).^{11,15} Thin-layer chromatography, high-performance liquid chromatography for mycolic acid identification, and gas chromatography for short-chain fatty acids (methyl esters) have been used to speciate mycobacterial isolates.^{1,11,14} Other tests are designed to detect common genetic changes associated with drug resistance, such as changes in the *katG* gene associated with isoniazid resistance and the *rpoB* gene associated with rifampin resistance.^{7,16-18} These tests offer clinicians a chance to know rapidly what organism they are treating and what drugs might be good initial choices.

TRANSMISSION

M. tuberculosis is transmitted from person-to-person by coughing or sneezing.^{2,7,13} This produces “droplet nuclei” that are dispersed in the air. Each droplet nuclei contains one to three organisms. Riley and colleagues showed that air circulated from a hospital TB ward could cause disease in guinea pigs.¹⁹ When this air was filtered or treated with ultraviolet radiation, the animals were not infected. Approximately 30% of individuals who experience prolonged contact with an infectious TB patient will become infected.

A person with cavitary, pulmonary TB and a cough may infect roughly one person per month until that person is treated effectively, although this number can vary significantly. A person with the uncommon laryngeal form of TB can spread organisms even when talking, so the transmission rates can be very high. HIV-infected patients acquire the organisms through the lungs just like normal hosts, but their weakened immune system puts them at very high risk for active disease.^{2,4,7,13}

PATHOPHYSIOLOGY

IMMUNE RESPONSE

Good T-lymphocyte responses are essential to controlling *M. tuberculosis* infections.^{2,7,20,21} In the mouse model, two different T-cell

responses—the T-helper type 1 (TH₁) response and the T-helper type 2 (TH₂) response—have been described. The TH₁ response is the preferred response to TB, and the TH₂ response, including the potentially subversive influence of interleukin (IL) 4, is undesirable.^{2,20,21} Some workers have argued that this dichotomy is clearer in the mouse model, and in many humans, the T-cell response may be classified as TH₀ (elements of both TH₁ and TH₂).²⁰ In either case, T-lymphocytes activate macrophages that, in turn, engulf and kill mycobacteria. T lymphocytes also destroy immature macrophages that harbor *M. tuberculosis* but are unable to kill the invaders.^{20,21} CD4+ cells are the primary T cells involved, with contributions by $\gamma\delta$ T cells and CD8+ T cells.²⁰ CD4+ T cells produce interferon γ (INF- γ) and other cytokines, including IL-2 and IL-10, that coordinate the immune response to TB.²⁰ Because CD4+ cells are depleted in HIV-infected patients, these patients are unable to mount an adequate defense to TB.^{20,21}

Although B-cell responses and antibody production can be demonstrated in TB-infected mammals, these humoral responses do not appear to contribute much to the control of TB within the host.^{2,7,20} T cells are responding to certain mycobacterial antigens, but the key antigen(s) invoking the immune response have not been identified.²⁰ Tumor necrosis factor- α (TNF- α) and INF- γ are important cytokines involved in coordinating the host's cell-mediated response. Rheumatoid arthritis patients treated with TNF- α inhibitors (infliximab) have high rates of reactivation TB.²² Therefore, patients known to be deficient in the activity of TNF- α or INF- γ should be screened for TB infection and offered appropriate treatment.

M. tuberculosis has several ways of evading or resisting the host immune response.^{20,21} In particular, *M. tuberculosis* can inhibit the fusion of lysosomes to phagosomes inside macrophages. This prevents the destructive enzymes found in the lysosomes from getting to the bacilli captured in the phagosomes. This stay of execution allows time for *M. tuberculosis* to escape into the cytoplasm. Virulent *M. tuberculosis* are able to multiply in the macrophage cytoplasm, thus perpetuating their spread. Finally, lipoarabinomannan, the principal structural polysaccharide of the mycobacterial cell wall, inhibits the host immune response.^{20,21} Lipoarabinomannan induces immunosuppressive cytokines, thus blocking macrophage activation; additionally, lipoarabinomannan scavenges O₂, thus preventing attack by superoxide anions, hydrogen peroxide, singlet oxygen, and hydroxyl radicals.^{20,21} These survival mechanisms make *M. tuberculosis* a particularly difficult organism to control. Any defects in the host immune system make it likely that *M. tuberculosis* will not be controlled and that active disease will ensue.

PRIMARY INFECTION

Primary infection usually results from inhaling airborne particles that contain *M. tuberculosis*.^{2,7,21} These particles, called *droplet nuclei*, contain one to three bacilli and are small enough (1 to 5 μ m) to reach the alveolar surface. Ingestion (swallowing) and inoculation (puncture wound) are other rare pathways to acquire *M. tuberculosis* infection.²¹

The progression to clinical disease depends on three factors: (a) the number of *M. tuberculosis* organisms inhaled (infecting dose), (b) the virulence of these organisms, and (c) the host's cell-mediated immune response.^{2,5,7,13,21,23} At the alveolar surface, the bacilli that were delivered by the droplet nuclei are ingested by pulmonary macrophages.²¹ If these macrophages inhibit or kill the bacilli, infection is aborted.²¹ If the macrophages cannot do this, the organisms continue to multiply. The macrophages eventually rupture, releasing many bacilli, and these mycobacteria are then phagocytized by other macrophages. This cycle continues over several weeks until the host is able to mount a more coordinated response.²¹ During this early phase of infection, *M. tuberculosis* multiplies logarithmically.²¹

Some of the intracellular organisms are transported by the macrophages to regional lymph nodes in the hilar, mediastinal, and retroperitoneal areas. The cycle of phagocytosis and cell rupture continues. During lymph node involvement, the mycobacteria may be held in check. More frequently, *M. tuberculosis* spreads throughout the body through the bloodstream.^{2,7,21} When this intravascular dissemination occurs, *M. tuberculosis* can infect any tissue or organ in the body. Most commonly, *M. tuberculosis* infects the posterior apical region of the lungs. This may be so because of the high oxygen content, and it may be because of a less-vigorous immune response in this area.

After about 3 weeks of infection, T lymphocytes are presented with *M. tuberculosis* antigens. These T cells become activated and begin to secrete INF- γ and the other cytokines noted earlier. The processes described in the immune response section earlier then begin to occur. First, T-lymphocytes stimulate macrophages to become bactericidal.²¹ Large numbers of activated microbicidal macrophages surround the solid caseous (cheese-like) tuberculous foci (the necrotic area of infection).²¹ This process of creating activated microbicidal macrophages is known as *cell-mediated immunity*.²¹

At the same time that cell-mediated immunity occurs, delayed-type hypersensitivity also develops through the activation and multiplication of T lymphocytes. Delayed-type hypersensitivity refers to the cytotoxic immune process that kills nonactivated immature macrophages that are permitting intracellular bacillary replication.²¹ These immature macrophages are killed when the T-lymphocytes initiate Fas-mediated apoptosis (programmed cell death).²¹ The bacilli released from the immature macrophages then are killed by the activated macrophages.²¹

By this time (>3 weeks), macrophages have begun to form granulomas to contain the organisms. In a typical tuberculous granuloma, activated macrophages accumulate around a caseous lesion and prevent its further extension.²¹ At this point, the infection is largely under control, and bacillary replication falls off dramatically. Depending on the inflammatory response, tissue necrosis and calcification of the infection site plus the regional lymph nodes may occur.

Over 1 to 3 months, activated lymphocytes reach an adequate number, and tissue hypersensitivity results. This is shown by a positive tuberculin skin test. Any remaining mycobacteria are believed to reside primarily within granulomas or within macrophages that have avoided detection and lysis, although some residual bacilli have been found in various types of cells.^{2,7,20}

Approximately 90% of infected patients have no further clinical manifestations. Most patients only show a positive skin test (70%), whereas some also have radiographic evidence of stable granulomas (approximately 20%). This radiodense area on chest radiograph is called a *Ghon complex*. Approximately 5% of patients (usually children, the elderly, and the immunocompromised) experience “progressive primary” disease that occurs before skin test conversion.^{24,25} This presents as a progressive pneumonia, usually in the lower lobes. Disease frequently spreads, leading to meningitis and other severe forms of TB.^{24,25} Because of this risk of severe disease, very young, elderly, and immunocompromised patients, including those with HIV, should be evaluated and treated for latent or active TB.

REACTIVATION DISEASE

6 Roughly 10% of infected patients develop reactivation disease at some point in their lives. Nearly half of these cases occur within 2 years of infection.^{2,7,13} In the United States, most cases of TB are believed to result from reactivation. Reinfection is uncommon in the United States because of the low rate of exposure and because previously sensitized individuals possess some degree of immunity to reinfection.^{2,21} Exceptions include patients coinfecting with HIV who live in areas of higher exposure to *M. tuberculosis*.

The apices of the lungs are the most common sites for reactivation (85% of cases).² This reflects the fact that *M. tuberculosis* prefers areas

with high oxygen content and possibly because the immune response may not be as effective in this region.^{2,21} For reasons that are not entirely known (waning cellular immunity, loss of specific T-cell clones, blocking antibody), organisms within granulomas emerge and begin multiplying extracellularly.²⁴ The inflammatory response produces caseating granulomas, which eventually will liquefy and spread locally, leading to the formation of a hole (cavity) in the lungs.

The immune response contributes to the severity of the lung damage. There is targeted killing of immature macrophages that are allowing mycobacterial multiplication (delayed-type hypersensitivity).^{20,21} In addition, there is “innocent bystander” killing of host cells and locally thrombosed blood vessels.²¹ The killing of mycobacteria, macrophages, and neutrophils that have entered the battle releases cytokines and lysozymes into the infectious foci. This toxic mixture can be too much for the surrounding alveoli and airway cells, causing regional necrosis and structural collapse.^{2,21} These unstable foci liquefy, spreading the infection to neighboring areas of the lung, creating a cavity. Some of this necrotic material is coughed out, producing droplet nuclei. Bacterial counts in the cavities can be as high as 10^8 per milliliter of cavitary fluid. Partial healing may result from fibrosis, but these lesions remain unstable and may continue to expand.^{2,21} If left untreated, pulmonary TB continues to destroy the lungs, resulting in hypoxia, respiratory acidosis, and eventually death.

EXTRAPULMONARY AND MILIARY TUBERCULOSIS

Caseating granulomas at extrapulmonary sites can undergo liquefaction, releasing tubercle bacilli and causing symptomatic disease.^{2,7} Extrapulmonary TB without concurrent pulmonary disease is uncommon in normal hosts but more common in HIV-infected patients. Because of these unusual presentations, the diagnosis of TB is difficult and often delayed in immunocompromised hosts.^{2,4,7} Lymphatic and pleural diseases are the most common forms of extrapulmonary TB, followed by bone, joint, genitourinary, meningeal, and other forms.^{2,7} Left untreated, these forms will spread to other organs and may result in death.

Occasionally, a massive inoculum of organisms enters the bloodstream, causing a widely disseminated form of the disease known as *miliary TB*. It is named for the millet seed appearance of the small granulomas seen on chest radiographs, and it can be rapidly fatal.²⁰ Miliary TB is a medical emergency requiring immediate treatment.

INFLUENCE OF HIV INFECTION ON PATHOGENESIS

3 HIV infection is the largest risk factor for active TB.^{2,7,20} As CD4+ lymphocytes multiply in response to the mycobacterial infection, HIV multiplies within these cells and selectively destroys them. In turn, the TB-fighting lymphocytes are depleted.²⁰ This vicious cycle puts HIV-infected patients at 100 times the risk of active TB compared with HIV-negative people.²⁵ In addition, the combination of HIV infection and certain social behaviors increases the risk of newly acquired TB. In selected areas of the United States, up to 50% of new TB cases are the result of recent infection, particularly among HIV-infected individuals.^{26–28}

As mycobacteria spread throughout the body, HIV replication accelerates in lymphocytes and macrophages. This leads to progression of HIV disease.^{20,29} HIV-infected patients who are infected with TB deteriorate more rapidly unless they receive antimycobacterial chemotherapy.^{30,31} Most clinicians elect to begin TB treatment first, and once this is under control, begin HIV treatment as well. Starting both treatments at the same time can lead to paradoxical worsening of the TB.^{13,32} This appears to result from a reinvigorated inflammatory response to TB. Because TB can be very dangerous in HIV-

positive patients, they should be screened for tuberculous infection or disease soon after they are shown to be HIV-positive.^{2,4,7,20}

CLINICAL PRESENTATION

The classical presentation of TB is shown below. The onset of TB may be gradual, and the diagnosis may not be considered until a chest radiograph is performed. Unfortunately, many patients do not seek medical attention until more dramatic symptoms, such as frank hemoptysis, occur. At this point, patients typically have large cavitory lesions in the lungs. These cavities are loaded with *M. tuberculosis*. Expectoration or swallowing of infected sputum may spread the disease to other areas of the body.^{1,2,7,23} Physical examination is nonspecific but suggestive of progressive pulmonary disease.

CLINICAL PRESENTATION OF TUBERCULOSIS

Signs and Symptoms

- Patients typically present with weight loss, fatigue, a productive cough, fever, and night sweats^{1,2,7,23}
- Frank hemoptysis

Physical Examination

- Dullness to chest percussion, rales, and increased vocal fremitus are observed frequently on auscultation

Laboratory Tests

- Moderate elevations in the white blood cell (WBC) count with a lymphocyte predominance

Chest Radiograph

- Patchy or nodular infiltrates in the apical areas of the upper lobes or the superior segment of the lower lobes^{2,7,23}
- Cavitation that may show air-fluid levels as the infection progresses

5 Patients coinfecting with HIV may have atypical presentations.^{1,2,7,23,33} As their CD4+ counts decline, HIV-positive patients are less likely to have positive skin tests, cavitory lesions, or fever. Pulmonary radiographic findings may be minimal or absent. HIV-positive patients have a higher incidence of extrapulmonary TB and are more likely to present with progressive primary disease. Because their symptoms are not specific to TB, a thorough workup for TB is essential.^{2,7,20,23}

Extrapulmonary TB typically presents as a slowly progressive decline in organ function.^{2,7,23} Patients may have low-grade fever and other constitutional symptoms. Patients with genitourinary TB may present with sterile pyuria and hematuria. Lymphadenitis often involves the cervical and supraclavicular nodes and may appear as a neck mass with spontaneous drainage. Tuberculous arthritis and osteomyelitis occur most commonly in the elderly and usually affect the lower spine and weight-bearing joints. TB of the spine is known as *Pott disease*.² Abnormal behavior, headaches, or convulsions suggest tuberculous meningitis. Involvement of the peritoneum, pericardium, larynx, and adrenal glands also occurs.^{2,7,23}

THE ELDERLY

5 TB in the elderly is easily confused with other respiratory diseases. Many clinical findings are muted or absent altogether. Compared with younger patients, TB in the elderly is far less likely to present with positive skin tests, fevers, night sweats, sputum production, or hemoptysis.^{2,23,34,35} Weight loss may occur but is nonspecific. In contrast, mental status changes are twice as common in the elderly, and mortality is six times higher.^{2,23,34} TB is a preventable cause of death in the elderly that should not be overlooked.

CHILDREN

5 TB in children, especially those younger than 12 years of age, may present as a typical bacterial pneumonia and is called *progressive primary TB*.^{23–25} Clinical disease often begins 1 to 2 months after exposure and precedes skin-test positivity. Unlike adults, pulmonary TB in children often involves the lower and middle lobes.^{23–25} Dissemination to the lymph nodes, gastrointestinal and genitourinary tracts, bone marrow, and meninges is fairly common. Because of delays in recruitment of cellular immunity, cavitory disease is infrequent, and the number of organisms present typically is smaller than in an adult. Because cavitory lesions are uncommon, children do not spread TB readily. However, TB can be rapidly fatal in a child, and it requires prompt chemotherapy.

DIAGNOSIS

SKIN TESTING

The key to stopping the spread of TB is early identification of infected individuals.^{1,2,7,23} Table 116–1 lists the populations most likely to benefit from skin testing (column 1 patients are at highest risk for TB, followed by those in column 2). Members of these high-risk groups should be tested for TB infection and educated about the disease.

The Mantoux test is the preferred TB skin test. It uses tuberculin purified protein derivative (PPD), and unlike the Heaf or tine test, the Mantoux test is quantitative. The standard 5-tuberculin-unit PPD dose is placed intracutaneously on the volar aspect of the forearm with a 26- or 27-gauge needle.^{2,23,30} This injection should produce a small, raised, blanched wheal. An experienced professional should read the test in 48 to 72 hours. The area of induration (the “bump”) is the important end point, not the area of redness. Table 116–1 lists the criteria for interpretation.^{1,2,7,23,30} The CDC does not recommend the routine use of anergy panels.^{30,36} Aplisol and Tubersol 5-tuberculin-unit products are available commercially, but because of more predictable results, Tubersol appears to be the preferred product.

The “booster effect” occurs in patients who do not respond to an initial skin test but show a positive reaction if retested about a week later.^{23,36} Patients with past *M. tuberculosis* infection and some patients with past immunization with bacillus Calmett -Guerin (BCG) vaccine or past infection with other mycobacteria may “boost” with a second skin test. Individuals who require periodic skin testing, such as healthcare workers, should receive a two-stage test initially.^{23,36,37} Once they are shown to be skin-test–negative, any positive skin test later shows recent infection, and this requires treatment.

The PPD skin test is an imperfect diagnostic tool. Up to 20% of patients with active TB are falsely skin-test–negative, presumably because their immune systems are overwhelmed.^{20,36} False-positive results are more common in low-risk patients and those recently vaccinated with BCG. Despite BCG vaccination, one should not ignore a positive PPD result. These patients require careful evaluation for active disease, and they may be offered preventive treatment because many come from areas where TB infection is common.

The QuantiFERON-TB Gold test measures the release of INF- γ in whole blood.³⁸ For latently infected persons, INF- γ is released in response to in vitro stimulation by PPD, whereas no release occurs in blood samples taken from uninfected persons. This test can provide a diagnosis of latent TB infection within hours, instead of the 2 to 3 days required for the traditional PPD skin test. Also, QuantiFERON-TB testing does not require a return visit by the patient to the clinic for reading of the PPD skin test, making it more convenient for the patient. Ongoing research seeks to find a diagnostic test that will confirm TB infection within minutes, allowing for immediate treatment decisions while the patient is still in the

TABLE 116-1 Criteria for Tuberculin Positivity by Risk Group

Reaction 5 mm of Induration	Reaction ≥ 10 mm of Induration	Reaction ≥ 15 mm of Induration
Human immunodeficiency virus (HIV)-positive persons Recent contacts of tuberculosis (TB) case patients Fibrotic changes on chest radiograph consistent with prior TB	Recent immigrants (i.e., within the last 5 y) from high-prevalence countries Injection-drug users Residents and employees ^a of the following high-risk congregate settings: prisons and jails; nursing homes and other long-term care facilities for the elderly; hospitals and other healthcare facilities; residential facilities for patients with acquired immunodeficiency syndrome (AIDS); homeless shelters Mycobacteriology laboratory personnel	Persons with no risk factors for TB
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/day of prednisone for 1 mo or more) ^b	Persons with the following clinical conditions that place them at high risk: silicosis; diabetes mellitus; chronic renal failure; some hematologic disorders (e.g., leukemias and lymphomas); other specific malignancies (e.g., carcinoma of the head or neck and lung); weight loss of $\geq 10\%$ of ideal body weight; gastrectomy; jejunioileal bypass Children younger than 4 y of age or infants, children, and adolescents exposed to adults at high risk	

^aFor persons who are otherwise at low risk and who are tested at the start of employment, a reaction of ≥ 15 mm induration is considered positive.

^bRisk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. *MMWR* 1995;44(RR-11):19–34.

clinic. Another related test, T-SPOT.TB, is available in Europe, and is undergoing review by the FDA here in the United States.³⁹

ADDITIONAL TESTS

When active TB is suspected, attempts should be made to isolate *M. tuberculosis* from the site of infection.^{2,7,23,36} Sputum collected in the morning usually has the highest yield.^{2,11,23} Daily sputum collection over 3 consecutive days is recommended.

For patients unable to expectorate, sputum induction with aerosolized hypertonic saline may produce a diagnostic sample. Bronchoscopy, or aspiration of gastric fluid via a nasogastric tube, may be attempted in selected patients.²³ For patients with suspected extrapulmonary TB, samples of draining fluid, biopsies of the infected site, or both may be attempted. Blood cultures are positive occasionally, especially in AIDS patients.^{23,33,40}

TREATMENT

Tuberculosis

■ DESIRED OUTCOMES

The desired outcomes for the treatment of tuberculosis are

1. Rapid identification of a new TB case
2. Initiation of specific antituberculosis treatment
3. Prompt resolution of the signs and symptoms of disease
4. Achievement of a noninfectious state in the patient, thus ending isolation
5. Adherence to the treatment regimen by the patient
6. Cure of the patient as quickly as possible (generally at least 6 months of treatment)

It is also important that patients with active disease are isolated to prevent spread of the disease and that appropriate samples for smears and cultures are collected. Secondary goals are identification of the index case that infected the patient, identification of all persons infected by both the index case and the new case of TB (“contact investigation”), and completion of appropriate treatments for those individuals.

■ GENERAL APPROACHES TO TREATMENT

Drug treatment is the cornerstone of TB management.^{2,7,13,41} Monotherapy can be used only for infected patients who do not have active TB (latent infection, as shown by a positive skin test). Once active disease is present, a minimum of two drugs, and generally three or four drugs, must be used simultaneously.^{2,7,13,41} The duration of treatment depends on the condition of the host, extent of disease, presence of drug resistance, and tolerance of medications. The shortest duration of treatment generally is 6 months, and 2 to 3 years of treatment may be necessary for cases of multidrug-resistant TB (MDR-TB).^{2,7,13,41} Because the duration of treatment is so long, and because many patients feel better after a few weeks of treatment, careful followup is required. Directly observed therapy by a healthcare worker is a cost-effective way to ensure completion of treatment.^{2,7,13,41–43}

■ PRINCIPLES FOR TREATING LATENT INFECTION AND FOR TREATING DISEASE

Asymptomatic patients with tuberculous infection have a bacillary load of about 10^3 organisms, compared with 10^{11} organisms in a patient with cavitary pulmonary TB.^{2,7,44} As the number of organisms increases, the likelihood of naturally occurring drug-resistant mutants also increases. Naturally occurring mutants are found at rates of 1 in 10^6 to 1 in 10^8 organisms for the antituberculosis drugs.^{2,41,44} When treating asymptomatic latent infection with isoniazid monotherapy, the risk of selecting out isoniazid-resistant organisms is low. The isoniazid mutation rate is about 1 in 10^6 , but only about 10^3 organisms are present in the body. In contrast, the risk of selecting out isoniazid-resistant organisms is unacceptably high in patients with cavitary TB. One can prevent selection of these resistant mutants by adding more drugs because the rates for resistance mutations to multiple drugs are additive functions of the individual rates. For example, only 1 in 10^{13} organisms would be naturally resistant to both isoniazid (1 in 10^6) and rifampin (1 in 10^7).^{2,41,44} It is unlikely that such rare organisms are present in a previously untreated patient.

Combination chemotherapy is required for treating active TB disease. The patient should receive at least two drugs to which the isolate is susceptible, and generally four drugs are given at the outset of treatment. Rifampin and isoniazid are the best drugs for preventing drug resistance, followed by ethambutol, streptomycin, and pyrazinamide.^{2,7,41,44,45}

Three subpopulations of mycobacteria are proposed to exist within the body, and each appears to respond to certain drugs.^{2,41,44} Most numerous are the extracellular, rapidly dividing bacteria, often found within cavities (about 10^7 to 10^9 organisms). These are killed most readily by isoniazid, followed by rifampin, streptomycin, and the other drugs. A second group resides within caseating granulomas (possibly 10^5 to 10^7 organisms). These organisms appear to be in a semidormant state, with occasional bursts of metabolic activity. Pyrazinamide, through its conversion within *M. tuberculosis* to pyrazinoic acid, appears most active against these organisms. Rifampin and isoniazid also may be active against this subpopulation. The third subset is the intracellular mycobacteria present within macrophages (10^4 to 10^6). Rifampin, isoniazid, and the quinolones appear to be most active against intracellular *M. tuberculosis*. While this appears to explain what happens during the treatment of TB, there is no practical way to quantitate these populations within a given patient.

■ NONPHARMACOLOGIC THERAPY

⑦ Nonpharmacologic interventions aim to (a) prevent the spread of TB, (b) find where TB has already spread using contact investigation, and (c) replenish the weakened (consumptive) patient to a state of normal weight and well-being. The first two items are performed by public health departments. Clinicians involved in the treatment of TB should verify that the local health department has been notified of all new cases of TB.

Workers in hospitals and other institutions must prevent the spread of TB within their facilities.^{2,4,13,30} All such workers should learn and follow each institution's infection control guidelines. This includes using personal protective equipment, including properly fitted respirators, and closing doors to "negative pressure" rooms. These hospital isolation rooms draw air in from surrounding areas rather than blowing air (and *M. tuberculosis*) into these surrounding areas. The air from the isolation room may be treated with ultraviolet lights and then vented safely outside. However, these isolation rooms work properly only if the door is closed.

Debilitated TB patients may require therapy for other medical problems, including substance abuse and HIV infection, and some may need nutritional support. Therefore, clinicians involved in substance abuse rehabilitation and nutritional support services should be familiar with the needs of TB patients.

Surgery may be needed to remove destroyed lung tissue, space-occupying infected lesions (*tuberculomas*), and certain extrapulmonary lesions.^{2,13,41} Vaccines against TB include BCG and *M. vaccae*.⁴¹ However, these vaccines are of limited value, and neither can prevent infection by *M. tuberculosis*. BCG (discussed below) may prevent

extreme forms of TB in infants, whereas *Mycobacterium vaccae* cannot be recommended.^{41,46}

■ PHARMACOLOGIC THERAPY

Treating Latent Infection

Isoniazid is the preferred drug for treating latent TB infection.^{2,7,13,41} Generally, isoniazid alone is given for 9 months. The treatment of latent TB infection (LTBI) reduces a person's lifetime risk of active TB from approximately 10% to approximately 1%. Because TB is spread easily through the air, each case prevented also prevents a second wave of cases that each prevented case would have produced. Historically, the treatment of LTBI has been called *prophylaxis*, *chemoprophylaxis*, or *preventive treatment*. By any name, it is one of the primary mechanisms for reducing TB in the United States. Table 116-2 lists the LTBI treatment options.

Because young children, the elderly, and HIV-positive patients are at greater risk of active disease once infected with *M. tuberculosis*, they require careful evaluation. Once active TB is ruled out, they should receive treatment for latent infection.^{2,22,23,41}

The keys to successful treatment of LTBI are (a) infection by an isoniazid-susceptible isolate, (b) adherence to the 9-month regimen, and (c) no exogenous reinfection.² Isoniazid adult doses are usually 300 mg daily (5 to 10 mg/kg of body weight)⁵⁵ (see Table 116-2). Lower doses are less effective.^{2,52} Isoniazid should be given on an empty stomach, and antacids should be avoided within 2 hours of dosing. When adherence is an issue, twice-weekly isoniazid (900 mg in an adult) can be given using directly observed treatment. Nine months of treatment is recommended, but 6 months still provides considerable benefit.

Rifampin 600 mg daily for 4 months can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid.^{2,25,51,52} Rifabutin 300 mg daily might be substituted for rifampin for patients at high risk of drug interactions. The combination of pyrazinamide plus rifampin is no longer recommended because of higher than expected rates of hepatotoxicity. When resistance to isoniazid and rifampin is suspected in the isolate causing infection, there is no regimen proved to be effective.^{2,41} Regimens that *might* be effective include ethambutol plus levofloxacin, but data regarding efficacy are lacking.

For recent skin-test converters of all ages, the risk of active TB outweighs the risk for drug toxicity.^{30,41} Pregnant women, alcoholics, and patients with poor diets who are treated with isoniazid should receive pyridoxine (vitamin B₆) 10 to 50 mg daily to reduce the incidence of central nervous system (CNS) effects or peripheral neu-

TABLE 116-2 Recommended Drug Regimens for Treatment of Latent Tuberculosis (TB) Infection in Adults

Drug	Interval and Duration	Comments	Rating ^a (Evidence) ^b	
			HIV-	HIV+
Isoniazid	Daily for 9 mo ^{c,d}	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or nonnucleoside reverse transcriptase inhibitors (NNRTIs)	A (II)	A (II)
	Twice weekly for 9 mo ^{c,d}	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 mo ^d	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 mo ^d	DOT must be used with twice-weekly dosing	B (II)	C (I)
Rifampin	Daily for 4 mo	For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide	B (II)	B (III)

^aStrength of recommendation: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given.

^bQuality of evidence: I, randomized clinical trial data; II, data from clinical trials that are not randomized or were conducted in other populations; III, expert opinion.

^cRecommended regimen for children younger than 18 years of age.

^dRecommended regimen for pregnant women. Some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

Adapted from Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(RR-6):31.

ropathies. All patients who receive treatment of LTBI should be monitored monthly for adverse drug reactions and for possible progression to active TB.

Treating Active Disease

8 The treatment of active TB requires the use of multiple drugs. There are two primary antituberculosis drugs, isoniazid and rifampin, with the rest of the drugs having specific roles.^{41,44,45} Isoniazid and rifampin should be used together whenever possible. Typically, *M. tuberculosis* is either very susceptible or very resistant to a given drug. This contrasts with *M. avium*, where moderately resistant organisms are a frequent occurrence. Theoretically, MIC results could be used to guide dosing in the treatment of moderately resistant *M. tuberculosis*, but this remains to be studied prospectively.^{2,13,41}

Drug-susceptibility testing should be done on the initial isolate for all patients with active TB. These data should guide the selection of drugs over the course of treatment.^{2,7,13,41} However, some patients are unable to provide a suitable specimen for laboratory testing. If susceptibility data are not available for a given patient, the drug-susceptibility data for the suspected source case or regional susceptibility data should be used.^{2,41}

Drug resistance should be expected in patients presenting for the retreatment of TB. These patients require retesting of drug susceptibility using freshly collected specimens. It is imperative to learn what drugs the patient received and for how long the patient received them.^{2,13,41} A treatment history, often called a “drug-o-gram,” shows the start and stop dates of all antimycobacterial drugs

on a horizontal bar graph.^{2,41} A “drug-o-gram” should be constructed for all retreatment patients.

10 The standard TB treatment regimen is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months, for a total of 6 months of treatment.^{2,13,41} If susceptibility to isoniazid, rifampin, and pyrazinamide is shown, ethambutol can be stopped at any time. Without pyrazinamide, a total of 9 months of isoniazid and rifampin treatment is required. Table 116-3 shows the recommended treatment regimens. When intermittent therapy is used, directly observed treatment is essential. Doses missed during an intermittent TB regimen decrease its efficacy and increase the relapse rate. Note that Table 116-3 shows recommendations that differ for HIV-negative and HIV-positive patients. HIV-positive patients should not receive highly intermittent regimens. In general, regimens given daily five times each week or three times weekly can be used for HIV-positive patients. Less-frequent dosing is associated with higher failure and relapse rates and the selection of rifampin-resistant organisms.⁴¹

CLINICAL CONTROVERSY

The recommended duration of treatment often is the same for HIV-negative and HIV-positive patients. However, some clinicians believe that therapy should be extended for patients with weakened immune systems. These clinicians treat HIV-positive patients with drug-susceptible TB for 9 months rather than the usual 6 months.

TABLE 116-3 Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Regimen	Drugs	Initial Phase Interval and Doses ^c (Minimal Duration)	Continuation Phase		Range of Total Doses (Minimal Duration)	Rating ^a (Evidence) ^b		
			Regimen	Drugs		Interval and Doses ^{c,d} (Minimal Duration)	HIV-	HIV+
1	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk) ^c	1a	Isoniazid/ rifampin	Seven days per week for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk) ^c	182–130 (26 wk)	A (I)	A (II)
			1b	Isoniazid/ rifampin	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II) ^f
			1c ^g	Isoniazid/ rifapentine	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 days/wk for 10 doses (2 wk) ^e then twice weekly for 12 doses (6 wk)	2a	Isoniazid/ rifampin	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II) ^f
			2b ^g	Isoniazid/ rifapentine	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	Isoniazid, rifampin, pyrazinamide, ethambutol	Three times weekly for 24 doses (8 wk)	3a	Isoniazid/ rifampin	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	Isoniazid, rifampin, ethambutol	Seven days per week for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk) ^c	4a	Isoniazid/ rifampin	Seven days per week for 217 doses (31 wk) or 5 days/wk for 155 doses (31 wk) ^e	273–195 (39 wk)	C (I)	C (II)
			4b	Isoniazid/ rifampin	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

^aRatings: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given; E, should never be given.

^bEvidence ratings: I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.

^cWhen directly observed therapy is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

^dPatients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

^eFive-day-a-week administration is always given by directly observed therapy. Rating for 5 day per week regimens is A(II).

^fNot recommended for HIV-infected patients with CD4+ cell counts <100 cells/ μ L.

^gOptions 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

From Centers for Disease Control and Prevention. *Treatment of tuberculosis. MMWR* 2003;52 (RR-11).

When a patient's sputum smears convert to a negative, the risk of the patient infecting others is greatly reduced, but it is not zero.^{2,21,41} Such patients can be removed from respiratory isolation, but they must be careful not to cough on others and should meet with others only in well-ventilated places. Smear-negative patients still may be culture-positive, so they still can transmit TB to others.

Patients who are slow to respond clinically, those who remain culture-positive at 2 months of treatment, those with cavitary lesions on chest radiograph, and perhaps HIV-positive patients should be treated for a total of 9 months and for at least 6 months from the time that they convert to smear and culture negativity.^{2,7,13,41} Some authors recommend therapeutic drug monitoring for such patients.^{2,41,45,47} When isoniazid and rifampin cannot be used, treatment durations become 2 years or more regardless of immune status.^{2,13,41,45}

Adjustments to the regimen should be made once the susceptibility data are available.^{2,13,41} If the organism is drug-resistant, careful consideration of the remaining therapeutic options must be made. Two or more drugs with *in vitro* activity against the patient's isolate and that the patient has not received previously should be added to the regimen, as needed.^{2,13,41} TB specialists should be consulted regarding cases of drug-resistant TB.^{2,13,41}

9 There is no standard regimen for MDR-TB.^{2,13,41} Each patient's exposure history, previous treatment history (including toxicity and adherence issues), and current susceptibility data must be considered simultaneously. *It is critical to avoid monotherapy, and it is critical to avoid adding a single drug to a failing regimen.*^{2,13,41} Adding one drug at a time leads to the sequential selection of drug resistance until there are no drugs left. The treatment of MDR-TB should be managed by TB specialists. It may take several months for a patient with MDR-TB to become culture-negative because the drugs used lack the potency of isoniazid and rifampin.^{2,44,45} Consequently, prolonged respiratory isolation may be required.

Drug resistance should be suspected in the following situations:

- Patients who have received prior therapy for TB
- Patients from areas with a high prevalence of resistance (New York City, Mexico, Southeast Asia, the Baltic countries, and the former Soviet states)
- Patients who are homeless, institutionalized, intravenous drug abusers, or infected with HIV
- Patients who still have acid-fast bacilli-positive sputum smears after 1 to 2 months of therapy
- Patients who still have positive cultures after 2 to 4 months of therapy
- Patients who fail treatment or relapse after treatment
- Patients known to be exposed to MDR-TB cases

The patients just listed should be considered infected with drug-resistant TB until proved otherwise. Empirical therapy with four or

more drugs may be needed for acutely ill patients.^{2,13,41} These regimens may be altered when the susceptibility pattern becomes known. If the index case is known, then the same effective regimen should be employed for the new case. Again, MDR-TB cases should be referred to specialists. A new term in use, "XDR-TB," refers to "extensively drug-resistant TB." Such organisms are resistant to at least isoniazid, rifampin, a fluoroquinolone and one second-line injectable drug (amikacin, capreomycin, or kanamycin).⁴⁸

Special Populations

Tuberculous Meningitis and Extrapulmonary Disease

Patients with CNS tuberculosis usually are treated for longer periods (9 to 12 months instead of 6 months) (Table 116-4).^{2,13,41} In general, isoniazid, pyrazinamide, ethionamide, and cycloserine penetrate the cerebrospinal fluid readily, but rifampin, ethambutol, and streptomycin have variable CNS penetration.⁴⁹ Of the quinolones, levofloxacin may be preferred based on current data. Extrapulmonary TB of the soft tissues can be treated with conventional regimens.^{2,13,41} TB of the bone typically is treated for 9 months, occasionally with surgical debridement.^{2,13,41}

Children TB in children may be treated with regimens similar to those used in adults, although some physicians still prefer to extend treatment to 9 months.^{2,13,23,24,41,50,51} Pediatric doses of isoniazid and rifampin on a milligram-per-kilogram basis are higher than those used in adults (Table 116-5).⁴¹

Pregnancy Women with TB should be cautioned against becoming pregnant because the disease poses a risk to the fetus and to the mother. If already pregnant, the usual treatment is isoniazid, rifampin, and ethambutol for 9 months.⁴¹ Isoniazid or ethambutol are relatively safe for use in pregnant women.^{2,41,49-51} B vitamins are particularly important during pregnancy and should be provided to women being treated for TB. Rifampin is associated rarely with birth defects, including limb reduction and CNS lesions.⁴⁹ In general, rifampin is used in pregnant women with TB. Pyrazinamide has not been studied in large numbers of pregnant women, but anecdotal data suggest that it may be safe.⁴¹

Streptomycin use during pregnancy may lead to hearing loss in the newborn, including complete deafness. Streptomycin and the other aminoglycosides must be reserved for critical situations where alternatives do not exist.^{2,41} Although the polypeptide capreomycin has not been studied, it probably carries the same risks.

Ethionamide may cause premature delivery and congenital deformities when used during pregnancy.^{41,49} Mongolism also has been reported with ethionamide, so it cannot be recommended in this setting. *p*-Aminosalicylic acid has been used safely in pregnancy, but specific data are lacking.^{41,49} Cycloserine is known to cross the placenta, but the effects on the developing fetus are not known. Therefore, cycloserine generally cannot be recommended during pregnancy.⁴⁹

TABLE 116-4 Evidence-Based^a Guidelines for the Treatment of Extrapulmonary Tuberculosis and Adjunctive Use of Corticosteroids^b

Site	Length of Therapy (mo)	Rating (Duration)	Corticosteroids ^c	Rating (Corticosteroids)
Lymph node	6	A(I)	Not recommended	D(III)
Bone and joint	6-9	A(I)	Not recommended	D(III)
Pleural disease	6	A(II)	Not recommended	D(I)
Pericarditis	6	A(II)	Strongly recommended	A(I)
CNS tuberculosis including meningitis	9-12	B(II)	Strongly recommended	A(I)
Disseminated disease	6	A(II)	Not recommended	D(III)
Genitourinary	6	A(II)	Not recommended	D(III)
Peritoneal	6	A(II)	Not recommended	D(III)

^aFor rating system, see Table 116-3.

^bDuration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known.

^cCorticosteroid preparations vary among studies.

TABLE 116-5 Doses^a of Antituberculosis Drugs for Adults and Children^b

Drug	Preparation	Adults/Children	Doses			
			Daily	1×/wk	2×/wk	3×/wk
First-line drugs						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for intravenous or intramuscular injection	Adults (max) Children (max)	5 mg/kg (300 mg) 10–15 mg/kg (300 mg)	15 mg/kg (900 mg) —	15 mg/kg (900 mg) 20–30 mg/kg (900 mg)	15 mg/kg (900 mg) —
Rifampin	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults ^c (max) Children (max)	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	— —	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	10 mg/kg (600 mg) —
Rifabutin	Capsule (150 mg)	Adults ^c (max) Children	5 mg/kg (300 mg) Appropriate dosing for children is unknown	— Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults Children	— The drug is not approved for use in children	10 mg/kg (continuation phase) (600 mg usual adult dose) The drug is not approved for use in children	— The drug is not approved for use in children	— The drug is not approved for use in children
Pyrazinamide	Tablet (500 mg, scored)	Adults Children (max)	1,000 mg (40–55 kg) 1,500 mg (56–75 kg) 2,000 mg (76–90 kg) ^k 15–30 mg/kg (2 g)	— — — —	2,000 mg (40–55 kg) 3,000 mg (56–75 kg) 4,000 mg (76–90 kg) ^k 50 mg/kg (2 g)	1,500 mg (40–55 kg) 2,500 mg (56–75 kg) 3,000 mg (76–90 kg) ^k —
Ethambutol	Tablet (100 mg, 400 mg)	Adults Children ^d (max)	800 mg (40–55 kg) 1,200 mg (56–75 kg) 1,600 mg (76–90 kg) ^k 15–20 mg/kg daily (1 g)	— — — —	2,000 mg (40–55 kg) 2,800 mg (56–75 kg) 4,000 mg (76–90 kg) ^k 50 mg/kg (2.5 g)	1,200 mg (40–55 kg) 2,000 mg (56–75 kg) 2,400 mg (76–90 kg) ^k —
Second-line drugs						
Cycloserine	Capsule (250 mg)	Adults (max) Children (max)	10–15 mg/kg/day (1 g in two doses), usually 500–750 mg/day in two doses ^e 10–15 mg/kg/day (1 g/day)	There are no data to support intermittent administration —	There are no data to support intermittent administration —	There are no data to support intermittent administration —
Ethionamide	Tablet (250 mg)	Adults ^f (max) Children (max)	15–20 mg/kg/day (1 g/day), usually 500–750 mg/day in a single daily dose or two divided doses ^f 15–20 mg/kg/day (1 g/day)	There are no data to support intermittent administration There are no data to support intermittent administration	There are no data to support intermittent administration There are no data to support intermittent administration	There are no data to support intermittent administration There are no data to support intermittent administration
Streptomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	^g 20–40 mg/kg/day (1 g)	^g —	^g 20 mg/kg	^g —
Amikacin-kanamycin	Aqueous solution (500-mg and 1-g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	^g 15–30 mg/kg/day (1 g) intravenous or intramuscular as a single daily dose	^g —	^g 15–30 mg/kg	^g —
Capreomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	^g 15–30 mg/kg/day (1 g) as a single daily dose	^g —	^g 15–30 mg/kg	^g —
<i>p</i> -Aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food; tablets (500 mg) are still available in some countries, but not in the United States; a solution for intravenous administration is available in Europe	Adults Children (max)	8–12 g/day in two or three doses 200–300 mg/kg/day in two to four divided doses (10 g)	There are no data to support intermittent administration There are no data to support intermittent administration	There are no data to support intermittent administration There are no data to support intermittent administration	There are no data to support intermittent administration There are no data to support intermittent administration
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500-mg vials) for intravenous injection	Adults Children	500–1,000 mg daily ^h	There are no data to support intermittent administration ^h	There are no data to support intermittent administration ^h	There are no data to support intermittent administration ^h

(continued)

TABLE 116-5 Doses^a of Antituberculosis Drugs for Adults and Children^b (continued)

Drug	Preparation	Adults/Children	Doses			
			Daily	1×/wk	2×/wk	3×/wk
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	<i>i</i>	<i>i</i>	<i>i</i>	<i>i</i>
Gatifloxacin	Tablets (400 mg); aqueous solution (200 mg/20 mL; 400 mg/40 mL) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	<i>i</i>	<i>i</i>	<i>i</i>	<i>i</i>

^aDose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

^bFor purposes of this document adult dosing begins at age 15 years.

^cDose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

^dThe drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to isoniazid or rifampin.

^eIt should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.

^fThe single daily dose can be given at bedtime or with the main meal.

^gDose: 15 mg/kg per day (1 g), and 10 mg/kg in persons older than 59 years of age (750 mg). Usual dose: 750–1,000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days/week and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

^hThe long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

ⁱThe long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

^jThe long-term (more than several weeks) use of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

^kMaximum dose regardless of weight.

Ciprofloxacin, levofloxacin, moxifloxacin, and the other quinolones are associated with permanent damage to cartilage in the weight-bearing joints of immature animals, especially dogs and rabbits.^{41,49} Although these drugs have not been shown to frequently cause joint problems in humans, other antituberculosis agents should be used during pregnancy.

Pregnant women with LTBI are not at the same level of risk compared with those with active disease. Therapy with isoniazid for LTBI may be delayed until after pregnancy or, if recent skin-test conversion has occurred, started during the second trimester of pregnancy.^{41,49–51} Although most antituberculosis drugs are excreted in breast milk, the amount of drug received by the infant through nursing is insufficient to cause toxicity. Quinolones should be avoided in nursing mothers, if possible.

HIV Infection Patients with AIDS and other immunocompromised hosts may be managed with chemotherapeutic regimens similar to those used in immunocompetent individuals, although treatment is often extended to 9 months (see Table 116-3).^{2,13,41} The precise duration to recommend remains a matter of debate. Highly intermittent regimens (twice or once weekly) are not recommended for HIV-positive TB patients. Prognosis has been particularly poor for HIV-infected patients infected with MDR-TB. Differentiation must be made between infection with *M. tuberculosis* and nontuberculous mycobacteria, such as MAC, because the drugs used are different. While awaiting laboratory results, the patient can be treated empirically for TB if there is any doubt about the causative organism. Some patients with AIDS malabsorb their oral medications; this is discussed under Therapeutic Drug Monitoring below.^{2,41,45,47} The major issue of drug interactions is discussed further below under Rifampin.

Renal Failure In nearly all patients, isoniazid and rifampin do not require dose modification in renal failure. They are eliminated primarily by the liver.^{45,49,52} In the unlikely event that peripheral neuropathies develop, the frequency of isoniazid dosing may be reduced. Pyrazinamide and ethambutol typically require a reduction in dosing frequency from daily to three times weekly (Table 116-6).^{41,52}

TABLE 116-6 Dosing Recommendations for Adult Patients with Reduced Renal Function and for Adult Patients Receiving Hemodialysis

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients with Creatinine Clearance <30 mL/min or for Patients Receiving Hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750–1,000 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week ^a
Ethionamide	No change	250–500 mg/dose daily
p-Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily)

Standard doses are given unless there is intolerance.

The medications should be given after hemodialysis on the day of hemodialysis.

Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.

Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing, using serum concentration monitoring.

^aThe appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity.

Renally cleared TB drugs include the aminoglycosides (amikacin, kanamycin, and streptomycin), capreomycin, ethambutol, cycloserine, and levofloxacin.^{41,49,52,53} Dosing intervals need to be extended for these drugs (see Table 116-6). Ciprofloxacin and moxifloxacin are approximately 50% cleared by the kidneys but may not require a change in dose from once daily, as used for TB. The metabolites of isoniazid, pyrazinamide, and *p*-aminosalicylic acid are cleared primarily by the kidneys. The role of these metabolites in causing toxicity is unknown, so their accumulation in renal failure may carry some risk.

Ethionamide and its sulfoxide metabolite are hepatically cleared, so dosing is unchanged.^{41,53} *p*-Aminosalicylic acid is converted largely to metabolites prior to renal elimination; these metabolites may accumulate in renal failure.⁵³ For patients on hemodialysis, the usual 12-hour dosing interval for *p*-aminosalicylic acid granules seems to be safe. Dialysis will remove the metabolites. Serum concentration monitoring must be performed for cycloserine to avoid dose-related toxicities in renal failure patients.^{45,47,53}

Hepatic Failure Antituberculosis drugs that rely on hepatic clearance for most of their elimination include isoniazid, rifampin, pyrazinamide, ethionamide, and *p*-aminosalicylic acid.⁴⁹ Ciprofloxacin and moxifloxacin are approximately 50% cleared by the liver. Elevations of serum transaminase concentrations generally are not correlated with the residual capacity of the liver to metabolize drugs, so these markers cannot be used as guides for drug dosing. Furthermore, isoniazid, rifampin, pyrazinamide, and, to a lesser degree, ethionamide, *p*-aminosalicylic acid, and, rarely, ethambutol may cause hepatotoxicity.^{41,45,49} For some patients with drug-susceptible TB, a “liver-sparing” regimen of streptomycin, levofloxacin, and ethambutol may be used, at least temporarily.^{41,45,49} Because this regimen requires 18 or more months of treatment to be successful, patients usually are switched to isoniazid- and rifampin-containing regimens as soon as they are able.

Morbid Obesity Data are not available for dosing the TB drugs in patients with morbid obesity.⁴⁹ Relatively hydrophilic drugs (isoniazid, pyrazinamide, the aminoglycosides, capreomycin, ethambutol, *p*-aminosalicylic acid, and cycloserine) can be dosed initially based on ideal body weight. Very low or very high serum concentrations can be avoided by checking the serum concentrations.

The TB Drugs

The interested reader is referred to several other publications for more detailed information regarding these drugs.^{2,12,41,44,45,47,49,54-56} Note that although the American Thoracic Society (ATS)/CDC guidelines recommend “maximum” doses, I disagree with this approach to therapy (see Table 116-5).⁴¹ In my view, the “maximum” dose for a given patient is the dose that produces the desired response with an acceptable level of toxicity.^{45,47} This can only be determined on a case-by-case basis. Artificially capping doses may deprive patients of needed drug.

Primary Antituberculosis Drugs Isoniazid. Isoniazid is one of the two most important TB drugs. It is highly specific for mycobacteria, with a MIC against *M. tuberculosis* of 0.01 to 0.25 mcg/mL. Most nontuberculous mycobacteria such as *M. avium* are resistant to isoniazid, although *M. kansasii* and *Mycobacterium xenopi* are susceptible. The most common mechanisms of resistance result from mutations in the *katG* or *inhA* genes.

Isoniazid is readily absorbed from the gastrointestinal tract and from intramuscular injection sites. It also can be given as a short intravenous infusion over 5 minutes if diluted in about 20 mL of normal saline.⁵⁷ Isoniazid should be given on an empty stomach whenever possible.⁵⁸ *N*-acetyltransferase 2 forms the principal metabolite acetylisoniazid, which lacks antimycobacterial activity. The rate at which humans acetylate isoniazid is determined genetically; slow

acetylation is an autosomal recessive trait and reflects a relative lack of *N*-acetyltransferase 2. Fast acetylators have isoniazid half-lives of less than 2 hours. Approximately 50% of whites and blacks and 80% to 90% of Asians and Eskimos are rapid acetylators. Slow acetylators have isoniazid half-lives of 3 to 4 hours and may be at an increased risk of neurotoxicity. The association of acetylator status and risk of hepatotoxicity, however, appears to be weak.⁵⁹ Poor absorption and rapid clearance of isoniazid in patients receiving highly intermittent therapy are associated with poor clinical outcomes.^{60,61}

Transient elevations of the serum transaminases occur in 12% to 15% of patients receiving isoniazid and usually occur within the first 8 to 12 weeks of therapy.⁴¹ Overt hepatotoxicity, however, occurs in only 1% of cases. Risk factors for hepatotoxicity include patient age, preexisting liver disease, excessive alcohol intake, pregnancy, and the postpartum state. Isoniazid also may result in neurotoxicity, most frequently presenting as peripheral neuropathy or, in overdose, as seizures and coma. Patients with pyridoxine deficiency, such as pregnant women, alcoholics, children, and the malnourished, are at increased risk. Isoniazid may inhibit the metabolism of phenytoin, carbamazepine, primidone, and warfarin.⁴⁵ Patients who are being treated with these agents should be monitored closely, and appropriate dose adjustments should be made when necessary.

Rifampin. The introduction of rifampin into routine use during the 1970s allowed for true short-course treatment of TB (6 to 9 months).^{2,13,41} Without rifampin, treatment is generally 18 months or longer. Drug resistance to rifampin is an ominous prognostic factor because it is frequently associated with isoniazid resistance and leaves the patient with few good therapeutic options. Clinicians *must* take care to protect susceptibility to rifampin by carefully treating their patients. Rifampin shows bactericidal activity against *M. tuberculosis* and several other mycobacterial species, including *M. bovis* and *M. kansasii*.⁶² Other nontuberculous mycobacteria, including MAC, show variable susceptibility to rifampin. Rifampin also is active against a broad array of other bacteria. Alteration of the target site on RNA polymerase, primarily through changes in the *rpoB* gene, leads to most forms of rifampin resistance.^{41,62}

Rifampin usually is given orally, but it also can be given as a 30-minute intravenous infusion.^{54,62} Oral doses are best given on an empty stomach.⁶³ Patients with AIDS, diabetes, and other gastrointestinal problems appear to have difficulty absorbing rifampin after oral doses, and this has been associated with therapeutic failures in some cases.^{45,47,61} Rifampin is metabolized to 25-desacetyl-rifampin, which retains most of rifampin’s activity; most of rifampin and its metabolite are cleared in the bile. Rifampin generally is given at 600 mg daily or intermittently, although this dose does not take full advantage of rifampin’s concentration-dependent killing.^{45,47} Higher doses should be tested in humans within the context of clinical trials.

CLINICAL CONTROVERSY

Rifampin shows concentration-dependent killing. Larger doses produce higher concentrations that more effectively kill bacteria and mycobacteria. High-dose rifampin fell out of favor because high doses given once or twice weekly caused flu-like symptoms. However, high doses (900 to 1,200 mg and possibly higher) can be given safely daily. Studies should be performed in humans with TB to take full advantage of rifampin’s potent activity.

Elevations in hepatic enzymes have been attributed to rifampin in 10% to 15% of patients, with overt hepatotoxicity occurring in less than 1%.^{41,62} More frequent adverse effects of rifampin include rash, fever, and gastrointestinal distress. Allergic reactions to rifampin have been reported and occur more frequently with intermittent rifampin doses 900 mg or more twice weekly. These reactions may

TABLE 116-7 Clinically Significant Drug–Drug Interactions Involving the Rifamycins

Drug Class	Drugs Whose Concentrations Are Substantially Decreased by Rifamycins (References)	Comments
Antiinfectives	HIV-1 protease inhibitors (saquinavir, indinavir, nelfinavir, amprenavir, ritonavir, lopinavir-ritonavir)	Can be used with rifabutin. Ritonavir, 400–600 mg twice daily, probably can be used with rifampin. The combination of saquinavir and ritonavir can also be used with rifampin.
	Nonnucleoside reverse transcriptase inhibitors (delavirdine, nevirapine, efavirenz)	Delavirdine should not be used with any rifamycin. Doses of nevirapine and efavirenz need to be increased if given with rifampin; no dose increase needed if given with rifabutin.
	Macrolide antibiotics (clarithromycin, erythromycin)	Azithromycin has no significant interaction with rifamycins.
	Doxycycline	May require use of a drug other than doxycycline.
Hormone therapy	Azole antifungal agents (ketoconazole, itraconazole, voriconazole)	Itraconazole, ketoconazole, and voriconazole concentrations may be subtherapeutic with any of the rifamycins. Fluconazole can be used with rifamycins, but the dose of fluconazole may have to be increased.
	Atovaquone	Consider alternate form of <i>Pneumocystis carinii</i> treatment or prophylaxis.
	Chloramphenicol	Consider an alternative antibiotic.
	Mefloquine	Consider alternate form of malaria prophylaxis.
Narcotics	Ethinylestradiol, norethindrone	Women of reproductive potential on oral contraceptives should be advised to add a barrier method of contraception when taking a rifamycin.
	Tamoxifen	May require alternate therapy or use of a nonrifamycin-containing regimen.
	Levothyroxine	Monitoring of serum thyroid-stimulating hormone recommended; may require increased dose of levothyroxine.
Anticoagulants	Methadone	Rifampin and rifapentine use may require methadone dose increase; rifabutin infrequently causes methadone withdrawal.
Immunosuppressive agents	Warfarin	Monitor prothrombin time; may require two- to threefold dose increase.
Anticonvulsants	Cyclosporine, tacrolimus	Rifabutin may allow concomitant use of cyclosporine and a rifamycin; monitoring of cyclosporine serum concentrations may assist with dosing.
	Corticosteroids	Monitor clinically; may require two- to threefold increase in corticosteroid dose.
Cardiovascular agents	Phenytoin, lamotrigine	Therapeutic drug monitoring recommended; may require anticonvulsant dose increase.
Bronchodilators	Verapamil, nifedipine, diltiazem (a similar interaction is also predicted for felodipine and nisoldipine)	Clinical monitoring recommended; may require change to an alternate cardiovascular agent.
	Propranolol, metoprolol	Clinical monitoring recommended; may require dose increase or change to an alternate cardiovascular drug.
	Enalapril, losartan	Monitor clinically; may require a dose increase or use of an alternate cardiovascular drug.
	Digoxin (among patients with renal insufficiency), digitoxin	Therapeutic drug monitoring recommended; may require digoxin or digitoxin dose increase.
	Quinidine	Therapeutic drug monitoring recommended; may require quinidine dose increase.
	Mexiletine, tocainide, propafenone	Clinical monitoring recommended; may require change to an alternate cardiovascular drug.
Sulfonylurea hypoglycemics	Theophylline	Therapeutic drug monitoring recommended; may require theophylline dose increase.
Hypolipidemics	Tolbutamide, chlorpropamide, glyburide, glimepiride, repaglinide	Monitor blood glucose; may require dose increase or change to an alternate hypoglycemic drug.
Psychotropic drugs	Simvastatin, fluvastatin	Monitor hypolipidemic effect; may require use of an alternate hypolipidemic drug.
Other Rifamycins	Nortriptyline	Therapeutic drug monitoring recommended; may require dose increase or change to alternate psychotropic drug.
	Haloperidol, quetiapine	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.
	Benzodiazepines (e.g., diazepam, triazolam), zolpidem, buspirone	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.

take the form of a flu-like syndrome with development of fever, chills, headache, arthralgias, and, rarely, hypotension and shock.^{41,55} Alternatively, hemolytic anemia or acute renal failure may occur, requiring permanent discontinuation.

Rifampin's potent induction of hepatic enzymes, especially cytochrome P450 3A4, may enhance the elimination of many other drugs, most notably the protease inhibitors used to treat HIV (Table 116-7). HIV-positive patients may benefit from the use of rifabutin instead of rifampin (see below).^{41,64-67} Also, women who use oral contraceptives must use another form of contraception during therapy because increased clearance of the hormones may lead to unexpected pregnancies. Patient records should be reviewed for potential drug interactions before dispensing rifampin.⁵⁴ Rifampin may turn urine and other secretions orange-red and may permanently stain some types of contact lenses.

Other Rifamycins. Rifabutin is used for disseminated *M. avium* infection in AIDS patients and is quite active against *M. tuberculosis*. Most rifampin-resistant organisms are resistant to rifabutin. Because rifabutin is a less-potent enzyme inducer than rifampin, it may be

used in patients who are receiving protease inhibitors.^{41,64-67} For HIV-positive patients, the ATS/CDC recommends regimens with three or more doses of the TB drugs per week (see Table 116-3). Rifapentine is a long-acting rifamycin that can be used once weekly in the continuation phase of treatment (after the first 2 months) in carefully selected HIV-negative patients. Rifapentine is approximately 85% as potent an enzyme inducer as rifampin, so similar drug interactions are likely.^{41,64-67}

Pyrazinamide. Adding pyrazinamide to the first 2 months of treatment with isoniazid and rifampin shortens the duration to 6 months for most patients.^{2,41} It is usually well absorbed and displays a fairly long half-life.^{68,69} The most common toxicities of pyrazinamide are gastrointestinal distress, arthralgias, and elevations in the serum uric acid concentrations.^{41,55} Most patients do not experience true gout. Hepatotoxicity is the major limiting adverse effect and is dose-related when pyrazinamide is given daily.

A fixed-combination product (Rifater, Aventis) of rifampin 120 mg, isoniazid 50 mg, and pyrazinamide 300 mg is designed to prevent drug resistance by keeping the self-medicating patient from using only one

drug at a time. If the patient is receiving directly observed treatment, there is no particular advantage to this product. The typical dose of Rifater will be five to six tablets daily. When pyrazinamide is discontinued after 2 months of treatment, the combination product Rifamate (isoniazid 150 mg and rifampin 300 mg) can be substituted.

Ethambutol. Ethambutol replaced *p*-aminosalicylic acid as a first-line agent in the 1960s because it was better tolerated by patients.^{2,41} Ethambutol is used as a fourth drug for TB while awaiting susceptibility data.⁴¹ If the organism is susceptible to isoniazid, rifampin, and pyrazinamide, ethambutol can be stopped. Ethambutol is active against most mycobacteria, including *M. tuberculosis* and *M. avium*, but it is generally bacteriostatic.

Ethambutol should not be given with antacids.⁷⁰ In patients with renal failure, the ethambutol dose should be reduced to three times per week.^{52,71} Retrobulbar neuritis is the major adverse effect. Patients may complain of a change in visual acuity, the inability to see the color green, or both. They should be monitored monthly while on the drug using Snellen wall charts for visual acuity and Ishihara red-green color discrimination cards.^{41,54,55}

Second-Line Antituberculosis Drugs Streptomycin. Streptomycin is one of three aminoglycoside antibiotics (along with amikacin and kanamycin) that are active against mycobacteria. Streptomycin is quite active against MAC and several other mycobacteria, enterococci, *Brucella*, *Yersinia*, and various other bacteria. Although labeled only for intramuscular dosing, streptomycin can be given safely as intravenous infusions (100 mL of dextrose 5% water or normal saline) over 30 minutes, similar to the other aminoglycosides.⁷² Streptomycin, like other aminoglycosides, is renally cleared by glomerular filtration and must be given less often in patients with renal dysfunction.^{41,45,54}

Streptomycin occasionally causes nephrotoxicity, although it tends to be mild and reversible. It also is capable of causing ototoxicity (vestibular and cochlear), which may become permanent with continued use.^{41,55} Older patients and those receiving long durations of treatment are most likely to experience hearing loss, whereas vestibular toxicity is highly unpredictable.

Resistance to amikacin and kanamycin is frequently linked but independent of resistance to streptomycin and independent of resistance to capreomycin. Therefore, susceptibility tests should guide the selection of these injectable drugs.

***p*-Aminosalicylic Acid.** In the United States, only the enteric-coated, sustained-release granule form (Paser) is available.^{73–75} Gastrointestinal disturbances are the most common adverse effects from *p*-aminosalicylic acid. Diarrhea is usually self-limited, with symptoms improving after the first 1 to 2 weeks of therapy. Occasionally, a few doses of an opioid will resolve the problem. It is also important to tell the patient that the empty granules will appear in the stool. Although FDA approved for three daily doses, pharmacokinetic data support twice-daily dosing.⁷⁴

Various types of malabsorption, including steatorrhea, were reported with previous dosage forms of *p*-aminosalicylic acid. Hypersensitivity may occur and, rarely, severe hepatitis. *p*-Aminosalicylic acid is known to produce goiter, with or without myxedema, that seems to occur more frequently with concomitant ethionamide therapy.

Cycloserine. Cycloserine is only used to treat MDR-TB. It is well absorbed orally and is best taken on an empty stomach.⁷⁶ It is cleared primarily through the kidneys by glomerular filtration and requires dosage reduction in renal failure. Cycloserine can produce dose-related CNS toxicity, including lethargy, confusion, or unusual behavior. Seizures, although reported, are exceedingly rare.^{2,41,54} Therapy is improved by maintaining 2-hour postdose serum concentrations between 20 and 35 mcg/mL.^{45,47} Most patients reach a maximum dose of 750 mg daily, divided unevenly into two doses.

This can be achieved by starting with 250 mg daily for 2 days, followed by 250-mg increments over 2-day intervals. This dose of cycloserine can be maintained if the patient complains of only occasional mild CNS effects, such as difficulty concentrating. Serum concentrations can be checked 1 to 2 weeks into therapy. The addition of pyridoxine 50 mg daily may improve patient tolerance of cycloserine.

Ethionamide. Ethionamide shares structural features with two other antimycobacterial agents, isoniazid and, more distantly, thiacetazone, a drug not used in the United States. Prothionamide, the *n*-propyl derivative of ethionamide, is used in Europe. Ethionamide is only active against organisms of the genus *Mycobacterium*, and it should be considered primarily bacteriostatic because it is difficult to achieve serum concentrations that would be bactericidal.^{41,45,47}

Gastrointestinal toxicity is the dose-limiting adverse effect. The drug should be introduced gradually in 250-mg increments, as described earlier for cycloserine. Rarely will a patient tolerate more than 1,000 mg daily in divided oral doses. Ethionamide may be administered with a light snack or prior to bedtime to minimize gastrointestinal intolerance. Food does not affect absorption significantly.⁷⁷ Little ethionamide is recovered in the urine, so doses remain the same in renal failure. Ethionamide may cause goiter, with or without hypothyroidism (especially when given with *p*-aminosalicylic acid), gynecomastia, alopecia, impotence, menorrhagia, photodermatitis, and acne. The management of diabetes also may be more difficult in patients receiving ethionamide. Because of these problems, ethionamide is only used when absolutely necessary.

Clofazimine. Clofazimine is a drug with good activity against *Mycobacterium leprae* and weak activity against *M. tuberculosis* and *M. avium*. It is used in doses of 100 to 200 mg daily in advanced cases of MDR-TB or MAC, especially when therapeutic options are limited.^{41,45} The drug has a terminal elimination half-life that is weeks long. Gastrointestinal distress and skin discoloration are the most important adverse reactions. Although uncommon, severe gastrointestinal pain may occur because of deposition of clofazimine crystals within the intestines; this may require surgical correction.

Thiacetazone. Thiacetazone is a weak agent used rarely in parts of the developing world because of its low cost. Skin reactions, including rash and Stevens-Johnson syndrome, may occur. Thiacetazone must be discontinued permanently as soon as a rash appears. Similar to trimethoprim-sulfamethoxazole, the incidence of skin reactions is much higher in AIDS patients.⁷⁸

Quinolones. Levofloxacin, ciprofloxacin, and moxifloxacin are sometimes used to treat MDR-TB. Moxifloxacin also is being studied as a possible replacement for certain first line agents.^{2,13,41,45,79} Quinolones are useful because most are available in oral and intravenous dosage forms, so they can be used in critically ill patients.

β -Lactam and β -Lactamase Inhibitor Combinations. The β -lactams have limited activity against mycobacteria because of β -lactamases and because β -lactams fail to enter macrophages.^{41,45,80} Cefoxitin, a β -lactamase-stable cephalosporin, has useful activity against rapidly growing mycobacteria, such as *M. fortuitum* and *Mycobacterium chelonae*. Combinations of β -lactam with β -lactamase inhibitors have been used in salvage regimens for TB patients with no other options, but are not used routinely to treat TB.

Macrolides/Azalides. The macrolide clarithromycin and azalide azithromycin represent substantial advances in the treatment of MAC but demonstrate limited activity against *M. tuberculosis* and are not used frequently for TB.^{2,13,41,45}

New Drugs and Delivery Systems. The nitroimidazopyran PA 824, which is chemically related to metronidazole and tinidazole, has activity against *M. tuberculosis* in vitro.^{81,82} This class, along with the oxazolidinones, may produce useful agents for TB. Linezolid has been

used in a few patients with TB.⁹⁶ Long-term use of linezolid requires careful monitoring of hematologic indices for potential anemia and thrombocytopenia. Although not proved conclusively, it may be possible to reduce the incidences of these toxicities by giving linezolid 600 mg daily for the slow-growing *M. tuberculosis* rather than the usual twice-daily dose used for gram-positive organisms. Chemical modification of existing compounds, such as pyrazinamide, may produce new TB drugs. Finally, continuing research on the construction of the mycobacterial cell wall and intracellular pathways may lead to agents with unique activity against this genus.

Liposomes have been investigated as delivery systems for various agents against mycobacteria, including isoniazid, rifampin, and the aminoglycosides. Liposomes also could be used to deliver β -lactams or other agents that generally are excluded from macrophages. By changing the pharmacokinetic profile of such agents, their use in the treatment of mycobacterial infections could be enhanced greatly. Currently, no such product is licensed for use against TB.

Corticosteroids. Adjunctive therapy with corticosteroids may be of benefit in some patients with tuberculous meningitis or pericarditis to relieve inflammation and pressure (see Table 116-4).^{2,41} They should be avoided in most other circumstances because they detract from the immune response to TB.

Bacille Calmette-Guérin Vaccine. The BCG vaccine is an attenuated, hybridized strain of *M. bovis*. It was developed in 1921 and is used as a prophylactic vaccine against TB. Administration of BCG vaccine is compulsory in many developing countries and is officially recommended in many others. Vaccination with BCG produces a subclinical infection resulting in sensitization of T lymphocytes and cross-immunity to *M. tuberculosis*, as well as cutaneous hypersensitivity and, in many cases, a positive tuberculin skin test.

In the published clinical trials, several different BCG preparations were used, and the efficacy of these vaccinations ranged from negative 56% (some patients did worse with the vaccine) to positive 80%.^{2,41} Trials within the United States and Puerto Rico have shown efficacy rates of 6% to 29%. The primary benefit of BCG vaccination appears to be the prevention of severe forms of TB in children. Data from the BCG trials show that the incidence of tuberculous meningitis and miliary TB is 52% to 100% lower and that the incidence of pulmonary TB is 2% to 80% lower in vaccinated children younger than 15 years of age than it was in unvaccinated controls.

Unfortunately, BCG does not appear to be very reliable in preventing disease by *M. tuberculosis* in other segments of the population. Side effects occur in 1% to 10% of vaccinated persons and usually include severe or prolonged ulceration at the vaccination site, lymphadenitis, and lupus vulgaris. It is recommended that pregnant women and patients with impaired immune systems, including those with HIV infection, avoid vaccination. The World Health Organization has recommended, however, that in populations where the risk of TB is high, HIV-infected infants who are asymptomatic should receive BCG vaccine at birth or as soon as possible thereafter. Because BCG infection has occurred in AIDS patients given the vaccine, individuals with symptomatic HIV infection should not be vaccinated.^{2,41}

In the United States, BCG vaccination is recommended only for uninfected children who are at an unavoidable risk of exposure to TB and for whom other methods of prevention and control have failed or are not feasible.^{2,41} Its use is very limited.

PHARMACOECONOMIC CONSIDERATIONS

The World Health Organization and the World Bank agree that the control of TB is one of the most cost-effective health interventions any nation can pursue. Early identification of TB cases and the effective use of isoniazid, rifampin, and pyrazinamide (plus ethambutol) while the isolate is still drug-susceptible always should be the

primary goals of public health departments. Contact investigation and treatment of those infected but without disease are important secondary goals to reduce the number of future cases.

Patients who complete all their treatment for drug-susceptible TB have cure rates over 95%. Noncompliance (nonadherence), drug resistance, extrapulmonary disease, and concomitant disease states reduce the overall effectiveness of chemotherapy of TB to approximately 75%.

The treatment of TB is not particularly expensive, especially if hospitalization is not required.⁸³ Furthermore, TB is quite curable. Because the various TB drugs each have a role to play in the treatment of TB or MDR-TB, all the antituberculosis drugs approved by the Food and Drug Administration should be on institutional formularies. Centers that see little MDR-TB need not keep stocks of the second-line drugs, provided that they are readily available should the need arise. Because the treatment of MDR-TB is difficult, and because missteps are potentially disastrous, such patients should be referred to centers experienced in the management of MDR-TB.^{2,41,84,85}

EVALUATION OF THERAPEUTIC OUTCOMES

MONITORING OF THE PHARMACEUTICAL CARE PLAN

The most serious problem with TB therapy is patient nonadherence to the prescribed regimens.^{86,87} Unfortunately, there is no reliable way to identify such patients a priori. In the study by Brudney and Dobkin,⁸⁶ 89% of the patients were noncompliant with therapy. It is critical to the control of TB that such adherence rates be improved dramatically. The most effective way to achieve this end is with directly observed treatment.^{2,13,41} Despite criticisms that it will cost more money, it is far cheaper in the long run to prevent the further spread of disease with directly observed treatment than to track down and treat additional cases of TB continuously.

The homeless and other underprivileged individuals are assumed to constitute the group of patients considered “unreliable,” and directly observed treatment should be reserved for them; it is also assumed that “responsible” patients cared for by private physicians may be treated with daily, unsupervised therapy. A study conducted in Baltimore, however, compared outcomes (sputum culture conversion to negative at 3 months) in patients with pulmonary TB who were treated by private physicians with outcomes in patients treated via directly observed treatment in a city-run clinic. Surprisingly, 3-month culture conversion occurred in only 40% of the private-care patients, compared with 90% in the city clinic-care patients.⁸⁸ Clearly, expansion of the use of directly observed treatment to nearly all patients with TB may be of benefit.

For patients who are acid-fast bacilli smear positive, they should have sputum samples sent for acid-fast bacilli stains every 1 to 2 weeks until two consecutive smears are negative. This provides early evidence of a response to treatment.⁴¹ Once on maintenance therapy, sputum cultures can be performed monthly until two consecutive cultures are negative, which generally occurs over 2 to 3 months. If sputum cultures continue to be positive after 2 months, drug susceptibility testing should be repeated, and serum concentrations of the drugs should be checked.

Serum chemistries, including blood urea nitrogen, creatinine, aspartate transaminase, and alanine transaminase, and a complete blood count with platelets should be performed at baseline and periodically thereafter, depending on the presence of other factors that may increase the likelihood of toxicity (e.g., advanced age, alcohol abuse, pregnancy).^{2,41} Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin concentration exceeds 3 mg/dL and in patients with symptoms such as nausea, vomiting, or jaundice. At this point, the offending agent(s) should be discontinued. Sequential reintroduc-

tion of the drugs with frequent testing of liver enzymes is often successful in identifying the offending agent; other agents may be continued. Alternative agents should be selected as needed. Audiometric testing should be performed at baseline and monthly in patients who must receive streptomycin for more than 1 to 2 months. Vision testing (Snellen visual acuity charts and Ishihara color discrimination plates) should be performed on all patients who receive ethambutol. All patients diagnosed with TB should be tested for HIV infection.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) or applied pharmacokinetics is the use of serum drug concentrations to optimize therapy.^{41,45,47,88,89} Non-AIDS patients with drug-susceptible TB generally do well, and TDM generally should be used if they are failing appropriate directly observed treatment (no clinical improvement after 2 to 4 weeks or smear-positive after 4 to 6 weeks). On the other hand, patients with AIDS, diabetes, cystic fibrosis, and various gastrointestinal disorders often fail to absorb these drugs properly and are candidates for TDM. Also, patients with hepatic or renal disease should be monitored, given their potential for overdoses.

In the treatment of MDR-TB, the differences between the maximum serum concentration (C_{max}) and the minimal inhibitory concentration (MIC) for the second-line agents are much smaller than with isoniazid and rifampin. Therefore, alterations in the absorption of these drugs can have significant impact on the outcome of therapy.^{45,47} Although the optimal serum concentrations for TB are not known, target serum peak concentrations have been proposed.^{45,47} Blood samples collected at 2 and 6 hours after a dose have been used with some success, although they may not be the optimal sampling times for all the drugs. Long-half-life drugs (e.g., pyrazinamide and cycloserine) can be sampled at 2 and 10 hours if an estimate of the half-life is desired. Finally, TDM of the TB and HIV drugs is perhaps the most logical way to untangle the complex drug interactions that take place (see Table 116-7).⁹¹

CLINICAL CONTROVERSY

Some TB centers employ TDM for many of their patients at the outset of treatment in order to identify drug-delivery problems early. Other centers wait to see how the patient responds and perform TDM only if problems arise. An argument can be made for either approach. The latter can save money, but delays in effective treatment can affect the patient's outcome adversely. Most otherwise healthy TB patients will absorb their drugs adequately. Patients who are critically ill or who have MDR-TB can benefit from early TDM.

CONCLUSIONS

Good patient adherence to treatment regimens is the cornerstone to effective antimycobacterial chemotherapy. Pharmacists should monitor TB therapy with particular interest in drug-drug interactions, drug malabsorption, and avoiding the error of adding a single drug to a failing regimen. They should educate patients on the importance of continuing their chemotherapy despite symptomatic improvement. Pharmacists should become part of a multidisciplinary team (with nurses, physicians, social workers) devoted to successful chemotherapy of TB patients and their families.

ABBREVIATIONS

ATS: American Thoracic Society
BCG: bacillus Calmette-Guérin

CDC: Centers for Disease Control and Prevention

INF: interferon

IL: interleukin

LTBI: latent tuberculosis infection

MAC: *Mycobacterium avium* complex

MDR: multidrug resistance

MIC: minimal inhibitory concentration

PPD: purified protein derivative

TB: tuberculosis

TDM: therapeutic drug monitoring

TH: T-helper cell

TNF: tumor necrosis factor

SI UNITS

Bilirubin

Total

Direct

Indirect

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