Chapter 135: Tuberculosis

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UPDATE SUMMARY

Update Summary

March 31, 2023

The following sections, tables, and figures were updated:

- The TB Drugs, Quinolones: Interim CDC guidance for the four-month regimen of moxifloxacin, rifapentine, isoniazid, pyrazinamide as a treatment option
- Diagnosis, Diagnostic Testing: Minor edits were made for clarity

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 50, Tuberculosis.

KEY CONCEPTS

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1. Tuberculosis (TB) is one of the most prevalent communicable infectious diseases on earth; and 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 the foreign born and other ethnic minorities, reflecting immigration patterns and greater ongoing transmission in these communities. Additional TB surveillance and preventive treatments are required within these communities.
3. TB is the leading cause of death in human immunodeficiency virus (HIV) infection worldwide. Coinfection with 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, older adults, 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 drugs in the treatment of TB. Organisms resistant to both these drugs (multidrug-resistant TB [MDR-TB]) are much more difficult to treat.
9. Directly observed treatment (DOT) should be used whenever possible to reduce treatment failures and the selection of drug-resistant isolates.
10. To avoid the development of resistance, never add a single drug to a failing TB treatment regimen.

BEYOND THE BOOK

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Read and review the study questions in the Self-Study Module 6 on Tuberculosis: Managing Tuberculosis Patients and Improving Adherence located on the Centers for Disease Control and Prevention (CDC) website: Self-Study Modules - Continuing Education Activities TB CDC Module6.pdf (cdc.gov). Focus on the Adherence to Treatment section (pages 27-55). This module is designed to teach healthcare providers about methods to improve medication adherence in different types of patients with tuberculosis disease. Strategies to improve patient adherence are described including directly observed therapy, incentives, and education. The module is a useful tool for students to enhance their understanding of assessment and implementation steps in the patient care process.

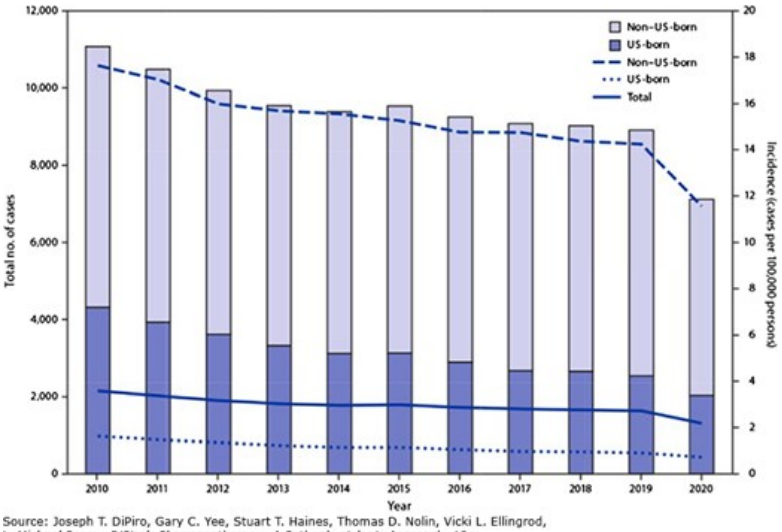
INTRODUCTION

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.[1] Given increasing drug resistance, it is critical that a major effort be made to control TB before the most potent drugs are no longer effective.

TB rates generally have risen with increasing urbanization and overcrowding because it is easier for an airborne disease to spread when people are living in closer proximity to each other. Hence, TB became a significant pathogen in Europe during the Middle Ages and peaked during the Industrial Revolution, when it caused significant mortality in Europe and in the United States.[1] 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 are used today. Unfortunately, in developing nations, some of these practices are not widely available, and TB continues to rage unabated (Fig. 135-1).

FIGURE 135-1

Reported tuberculosis cases in the United States. (Note: Number of tuberculosis cases among persons with unknown origin are not shown [range = 2-61]. Total rate includes cases among persons with unknown national origin. Rates for non–US-born and US-born persons were calculated by using midyear Current Population Survey estimates. Total rate was calculated by using midyear population estimates from the US Census Bureau.) *(Reprinted from reported Tuberculosis in the United States, 2017. Atlanta, GA: US Department of Health and Human Services, CDC; 2018.)*



EPIDEMIOLOGY

Over one-fourth of the world's population is infected by *M. tuberculosis*.[1] In 2019, there were about 10 million new cases and 1.2 million deaths from TB reported.[1] In the United States, 9 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.[2] In 2019, 8,916 new TB cases were reported in the United States.[2] A further drop occurred in 2020, driven largely by measures to prevent another respiratory pathogen, COVID-19.[3] TB cases in the United States declined by approximately 5% per year from 1953 to 1983.[2] Starting in 1984, cases plateaued, and then rose from 1988 to 1992.[2] Since 1993, more effective infection control practices and treatment protocols have reduced TB rates significantly. However, the eradication of TB from the United States remains difficult because it is tied to immigration from high incidence countries.[1–3]

Risk Factors for Infection

Location and Place of Birth

California, Florida, New York, and Texas accounted for just over half of the TB cases reported nationally in 2019.[3] Within these states, TB is most prevalent in large urban areas and among those born outside the United States in high TB incidence countries.[3]

The percentage of foreign-born persons with TB in the United States has increased annually, reaching 71% in 2019.[3] In 2019, over half of foreign-born persons with TB originated from five countries: Mexico, the Philippines, India, Vietnam, and China.[3] Healthcare workers must consider TB when caring

for patients from these countries who experience symptoms such as cough, fever, and weight loss. Furthermore, foreign-born persons account for almost 90% of the multidrug-resistant (MDR) TB cases in the United States.[3]

Close contacts of pulmonary TB patients such as family members, coworkers, or coresidents in places such as prisons, shelters, or nursing homes are most likely to become infected. The more prolonged the contact, the greater is the risk, with infection rates as high as 30%.[2,3] People with TB frequently have limited access to healthcare, live in crowded conditions, or are homeless.[2,3] Many have histories of alcohol use disorder or illicit drug use, and are coinfected with hepatitis B or HIV. These concurrent social and health problems make treating some TB patients particularly challenging.

Ethnicity and Age

2 In the United States, TB disproportionately affects the foreign-born and other ethnic minorities. In 2019, Asians accounted for 36% percentage of total TB cases; Hispanic/Latino people for 30%, and Blacks 20%.[3] Non–US-born persons had a TB rate 15.5 times greater than the rate among US-born persons.[3] These disparities are the result of a complex interplay of social and environmental factors including urbanization, access to healthcare, poverty, and migration.[3–5]

In 2019, the number of TB cases was highest in the 25- to 44-year and the 45- to 64-year-age groups, while the rate per 100,000 population was highest in those over 65 years of age.[3] The overall TB incidence was 2.7 per 100,000 population.[3]

Coinfection with Human Immunodeficiency Virus

3 In patients who have LTBI, human immunodeficiency virus (HIV) is the most important risk factor, especially for people between the ages of 25 and 44 years.[4] TB and HIV act synergistically within patients and across populations, making each disease worse than it might otherwise be. In 2019, 4.9% of TB patients with known HIV statues were coinfected, with about 7.8% in the 25- to 44-year age group.[3,4,6] HIV coinfection may not increase the risk of acquiring *M. tuberculosis* infection, but it does increase the likelihood of progression to active disease.[4] There are higher mortality rates in persons coinfected with HIV and MDR or and extensively drug-resistant (XDR) TB.[6]

Risk Factors for Disease

Once infected with *M. tuberculosis*, a person's lifetime risk of active TB is approximately 10%.[2–4] The greatest risk for active disease occurs during the first 2 years after infection. Children younger than 2 years and adults older than 65 years have two to five times greater risk for active disease compared with other age groups. Patients with underlying immune suppression (eg, renal failure, cancer, and immunosuppressive drug treatment) have 4 to 16 times greater risk than other patients.[6] HIV-infected patients with *M. tuberculosis* infection are 100 times more likely to develop active TB than normal hosts.[6] HIV-infected patients have an annual risk of active TB of approximately 10%, rather than a lifetime risk at that rate.[6] Therefore, all patients with HIV infection should be screened for TB 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.[7] It is 1 to 4 μm in length, and under the microscope, it is either straight or slightly curved in shape.[7] It does not stain well with Gram stain, so the Ziehl–Neelsen stain or the fluorochrome stain must be used instead.[7] After Ziehl–Neelsen staining with carbol-fuchsin, mycobacteria retain the red color despite acid–alcohol washes. Hence, they are called *acid-fast bacilli* (AFB).[7] On culture, *M. tuberculosis* grows slowly, doubling about every 20 hours. This is slow compared with gram-positive and gram-negative bacteria, which double about every 30 minutes.

Culture and Susceptibility Testing

All clinical specimens suspected of containing mycobacteria should be cultured. Culture is required for species identification and for drug-susceptibility testing.

Direct susceptibility testing involves inoculating specialized media with organisms taken directly from a concentrated, smear-positive specimen.[7] This approach produces susceptibility results in 2 to 3 weeks. Culture-based phenotypic drug-susceptibility testing methods are the primary methods for drug-resistance detection. These methods are time consuming and require sophisticated laboratory infrastructure. Direct susceptibility testing uses critical concentrations of antituberculosis drugs to determine resistance of an isolate. A critical concentration is a previously established breakpoint separating "susceptible" from "resistant." Indirect susceptibility testing involves inoculating the test media with organisms obtained from a pure culture of the organisms, which can take several more weeks.[1,7]

The most common agar method has limitations which include length of time to obtain results, drug degradation during incubation, and a qualitative result (susceptible or resistant). The newer mycobacterial growth indicator tube (MGIT, Becton Dickson, Sparks, MD) systems use liquid media and detect live mycobacteria in as few as 9 to 14 days.[8,9]

Rapid identification tests are now available, but cost and care of equipment remain an issue in many parts of the world.[7–10] The Enhanced Amplified *Mycobacterium tuberculosis* Direct test has been approved for use by the US Food and Drug Administration (FDA) in AFB smear-positive and smear-negative specimen in patients with fewer than 7 days of antimycobacterial therapy and the Gene Xpert MTB/RIF assay in patients with fewer than 3 days of treatment.[10–12] The Amplicor *Mycobacterium tuberculosis* test has been approved for smear-positive samples.[8,9]

The Hain test, a line-probe assay that diagnoses resistance to isoniazid and rifampin by detecting several gene mutations responsible for drug resistance, has also entered into limited clinical use in the United States.[9] The Gene X-pert MTB/RIF test simultaneously identifies *M. tuberculosis* and rapidly determines if resistance to rifampin is present.[10–12] The test has excellent performance in both smear-positive and -negative patients, and high accuracy for determination of rifampicin resistance.[10,12] Colorimetric redox indicator and nitrate reduction assays for rapid detection of rifampicin and isoniazid resistance are both inexpensive and have rapid turnaround times of 1 week. Microscopic observation drug-susceptibility assay is a simple test using sputum samples to detect characteristic patterns of growth of *M. tuberculosis* and resistance patterns.[10,12] Time to diagnosis is 7 days and drug susceptibilities are available at the time of diagnosis.[12] Most patients with microscopic observation drug-susceptibility assays are diagnosed within 2 weeks, and it is similarly efficient irrespective of bacterial burden.[13]

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.[9,14] Mutations that affect the *rpoB* gene alter the protein structure of the target so that rifampin cannot bind; thus, conferring resistance. Similarly, isoniazid-resistant isolates can be detected by sequencing the *inhA* gene which leads to overproduction of the drug target and mutations in *katG* gene which inhibits activation of isoniazid prodrug. Probe assays do not eliminate the need for conventional culture and susceptibility testing; conventional drug-susceptibility testing is needed to diagnose XDR-TB. The decision to use nucleic acid amplification tests should be individualized.[9,14] Advanced sequencing techniques continue to evolve.

Transmission

M. tuberculosis is transmitted from person to person by coughing or other activities that cause the organism to be aerosolized.[15] These particles, called *droplet nuclei,* contain one to three bacilli and are small enough (1-5 mm) to reach the alveolar surface.[16] Approximately 30% of individuals who experience prolonged contact with an infectious TB patient will become infected.[15]

A person with cavitary, pulmonary TB and a cough is considered infectious and may infect greater than 30% of contacts until that person is treated effectively, although this percentage and the absolute 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 even higher.[15,16]

The National TB Molecular Surveillance Center performs whole genome sequencing on isolates of *M. tuberculosis* gathered from newly diagnosed patients in the United States. Samples are submitted by contracted laboratories and then genotype results are loaded into the system to identify chains of transmission and outbreaks.[9] Public health interventions can be targeted and cases that are the same cluster are likely to be related and treated similarly.[9]

PATHOPHYSIOLOGY

Immune Response

T-lymphocyte responses are essential to controlling *M. tuberculosis* infections.[15,16] In the mouse model, two different T-cell responses—the T-helper type 1 (TH_1) response and the T-helper type 2 (TH_2) response—have been described. The TH_1 response is the preferred response to TB, and the TH_2 response, including the potentially subversive influence of interleukin (IL) 4, is undesirable.[15,16] This dichotomy is clearer in the mouse model, and in many humans, the T-cell response may be classified as TH_0 (elements of both TH_1 and TH_2).[15,16] 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.[15,16] CD4+ cells are the primary T cells involved, with contributions by γ δ T cells and CD8+ T cells.[15] CD4+ T cells produce INF-*γ* and other cytokines, including IL-2 and IL-10, that coordinate the immune response to TB.[15,16] Because CD4+ cells are depleted in HIV-infected patients, these patients are unable to mount an adequate defense to TB.[15,16]

Although B-cell responses and antibody production can be demonstrated in TB-infected mammals, these humoral responses may not contribute much to the control of TB within the host.[16] Tumor necrosis factor-*α* (TNF-*α*) and INF-*γ* are important cytokines involved in coordinating the host's cell-mediated response.[17] Rheumatoid arthritis patients treated with TNF-*α* inhibitors (such as infliximab) have high rates of reactivation TB.[17] Therefore, patients 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.[16] In particular, *M. tuberculosis* can inhibit the fusion of lysosomes to phagosomes inside macrophages, preventing the destructive enzymes found in the lysosomes from getting to the bacilli captured in the phagosomes. This inhibition of destructive mechanisms allows time for *M. tuberculosis* to escape into the cytoplasm. Virulent *M. tuberculosis* bacilli are able to multiply in the macrophage cytoplasm, thus perpetuating their spread. Finally, lipoarabinomannan (LAM), the principal structural polysaccharide of the mycobacterial cell wall, inhibits the host immune response.[16] LAM induces immunosuppressive cytokines, thus blocking macrophage activation; additionally, LAM scavenges O_2, thus preventing attack by superoxide anions, hydrogen peroxide, singlet oxygen, and hydroxyl radicals.[16] 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.*[16,18] 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.[16,18] At the alveolar surface, the bacilli that were delivered by the droplet nuclei are ingested by pulmonary macrophages. If these macrophages inhibit or kill the bacilli, infection is aborted.[16] 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.[16,18] During this early phase of infection, *M. tuberculosis* multiplies logarithmically.[16]

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.[15,16] 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 or less vigorous immune response in this area.[15,18]

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 above then begin to occur.[15] First, T lymphocytes stimulate macrophages to become bactericidal.[15,16] Large numbers of activated microbicidal macrophages surround the solid caseous (cheese-like) tuberculous foci (the necrotic area of infection).[15,16] This process of creating activated microbicidal macrophages is known as cell-mediated immunity.[16]

When cell-mediated immunity occurs, delayed-type hypersensitivity (DTH) also develops through the activation and multiplication of T lymphocytes. DTH refers to the cytotoxic immune process that kills nonactivated immature macrophages that are permitting intracellular bacillary replication.[16] These immature macrophages are killed when the T lymphocytes initiate Fas-mediated apoptosis (programmed cell death).[16] The bacilli released from the immature macrophages then are killed by the activated macrophages.[16]

After 3 weeks, in most recently infected individuals, 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.[16] 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. In practical terms, this is the reason why tests to diagnose LTBI, purified protein derivative (PPD) skin test, and the INF-γ release assays take between 2 and 12 weeks to become positive. 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.[7,15]

Approximately 90% of infected patients have no further clinical manifestations. Most patients only show a positive skin or blood test for immune response (70%), whereas some also have radiographic evidence of stable granulomas.[18] This radiodense area on chest radiograph is called a *Ghon's complex*. Approximately 5% of patients (usually children, older adults, and the immunocompromised) experience "progressive primary" disease that occurs before skin test conversion, which presents as a progressive pneumonia, usually in the lower lobes.[18] Disease frequently spreads, leading to meningitis and other severe forms of TB.[18,19] Because of this risk of severe disease, young, elderly, and immunocompromised patients, including those with HIV, should be evaluated and treated for latent or active TB.[18,19]

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.[15,18] In the United States, most cases of TB 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.[15,18] Exceptions include patients coinfected 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).[15,18] 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.[15,18] 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, and DTH allows for intracellular mycobacterial multiplication.[15,16] In addition, there is "innocent bystander" killing of host cells and locally thrombosed blood vessels.[15] 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.[15] 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 (or 10^{11}/L) of cavitary fluid. Partial healing may result from fibrosis, but these lesions remain unstable and may continue to expand.[15] 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.[15] 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.[15] Lymphatic and pleural diseases are the most common forms of extrapulmonary TB, followed by bone, joint, genitourinary, meningeal, and other forms.[15] 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.[15] Miliary TB is a medical emergency requiring immediate treatment.

Influence of Human Immunodeficiency Virus Infection on Pathogenesis

3 HIV infection is the strongest single risk factor for progressing to active TB.[15,18] 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.[15,18] This vicious cycle puts HIV-infected persons at 100 times the risk of active TB compared with HIV-negative people.[20,21] In addition, the combination of HIV infection and certain social behaviors increases the risk of newly acquired TB. In select areas of the United States during the resurgence of TB during the early 1990s, up to 50% of new TB cases were the result of recent infection, particularly among HIV-infected individuals.[1,20,21]

As mycobacteria spread throughout the body, HIV replication accelerates in lymphocytes and macrophages. This leads to progression of HIV disease.[15,20,21] HIV-infected persons who are infected with TB deteriorate more rapidly unless they receive antimycobacterial chemotherapy.[20,21] Most clinicians now recommend integrated antiretroviral therapy beginning TB treatment first, and then beginning HIV treatment within 2 to 12 weeks.[22–24] However, the timing needs to be individualized based on degree of immunosuppression from HIV and the individual's tolerance of the treatment regimen. Immune reconstitution inflammatory syndrome or a paradoxical worsening of TB can occur, especially in persons with more severe immunosuppression; this results from a reinvigorated inflammatory response to TB.[22,24] HIV-positive persons should be screened for tuberculous infection or disease soon after they are shown to be HIV positive.[22]

CLINICAL PRESENTATION

The classical presentation of TB is weight loss, fatigue, a productive cough, fever, and night sweats. The onset of TB may be gradual, and the diagnosis may not be considered until a chest radiograph is performed. Unfortunately, many people do not seek medical attention until more dramatic symptoms, such as hemoptysis, occur. At this point, infected persons typically have large cavitary 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.[15,18,25] Physical examination is nonspecific but can be suggestive of progressive pulmonary disease.

Human Immunodeficiency Virus

5 Persons coinfected with HIV may have atypical presentations.[20–22,25] As their CD4+ counts decline, HIV-positive individuals are less likely to have positive skin tests, cavitary lesions, or fever. Pulmonary radiographic findings may be minimal or absent. HIV-positive persons 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.[21,22]

Extrapulmonary

Extrapulmonary TB typically presents as a slowly progressive decline in organ function.[15,18–20] Infected persons may have low-grade fever and other constitutional symptoms. Those 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 older adults and usually affect the lower spine and weight-bearing joints. TB of the spine is known as *Pott's disease*.[15] Abnormal behavior, headaches, or convulsions suggest tuberculous meningitis. Involvement of the peritoneum, pericardium, larynx, and adrenal glands also occurs.[15,19]

Older Adults

5 TB in the older adults is easily confused with other respiratory diseases. Many clinical findings are muted or absent altogether. Compared with younger patients, TB in the older adults is far less likely to present with positive skin tests, fevers, night sweats, sputum production, or hemoptysis.[15,18,25] Weight loss may occur but is nonspecific. In contrast, mental status changes are twice as common in older adults, and mortality is six times higher.[15,18] TB is a preventable cause of death in older adults that should not be overlooked.

Children

5 TB in children, especially those younger than 12 years, may present as a typical bacterial pneumonia and is called *progressive primary TB*.[18,19,25] 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.[18,19] Dissemination to the lymph nodes, gastrointestinal (GI) and genitourinary tracts, bone marrow, and meninges is common. Because of delays in recruitment of cellular immunity, cavitary disease is infrequent, and the number of organisms present typically is smaller than in an adult. Because cavitary lesions are uncommon, children do not spread TB readily. However, TB can be rapidly fatal in a child, and it requires prompt chemotherapy.

CLINICAL PRESENTATION: Tuberculosis

Signs and Symptoms

- Patients typically present with cough, weight loss, fatigue, fever, and night sweats.[2,15,16]
- Frank hemoptysis usually occurs late in the course of disease but may present earlier.

Physical Examination

- Dullness to chest percussion, rales, and increased vocal fremitus are observed frequently on auscultation but a normal lung examination is common compared to the degree of radiological lung involvement.
- Patient is usually thin with evidence or recent weight loss.

Laboratory Tests

- Moderate elevations in the white blood cell count with a lymphocyte predominance.
- High platelet count (thrombocytosis) and mild-to-moderate anemia are common.

Diagnostic Considerations

- Positive-sputum smear
- Fiber-optic bronchoscopy (if sputum tests are inconclusive and suspicion is high)

Chest Radiograph

- Patchy or nodular infiltrates in the apical areas of the upper lobes or the superior segment of the lower lobes.[2,15,16]
- Cavitation that may show air–fluid levels as the infection progresses.

DIAGNOSIS

The following section focuses on diagnostic testing for infection with *M. tuberculosis*. If active disease is suspected based on clinical presentation, additional diagnostic tests are also reviewed to confirm active disease.

Diagnostic Testing

The key to stopping the spread of TB is early identification of infected individuals.[25] Table 135-1 lists the populations most likely to benefit from testing (column 1 persons 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.

TABLE 135-1

Criteria for Tuberculosis Positivity

Reaction ≥5 mm of Induration	Reaction ≥10 mm of Induration	Reaction ≥15 mm of Induration
HIV-infected persons A recent contact of a person with TB disease Fibrotic changes on chest radiograph consistent with prior TB Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/day or more of prednisone for 1 month or longer, taking TNF-α antagonists)[b]	Recent immigrants (ie, within the last 5 years) 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 facilities for the elderly, hospitals and other healthcare facilities, residential facilities for patients with AIDS, and homeless shelters Mycobacteriology laboratory personnel, persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders, other specific malignancies, gastrectomy, and jejunoileal bypass Children younger than 5 years of age or infants, children, and adolescents exposed to adults at high risk	Persons with no risk factors for TB

Interpretation of IGRA Results

The interpretation of IGRAs is based on the amount of IFN-γ, in T-SPOT®.TB. An IGRA is recommended over a TST in persons at least 5 years of age who are likely to have *M. tuberculosis* infection; who are at low or moderate risk of the disease progressing; in whom it has been determined that LTBI testing is necessary; and who have been vaccinated against Calmette-Guérin or are not likely to return for follow-up after a TST. The TST is a viable second option in certain circumstances, such as if an IGRA is unavailable. Laboratories should provide both the qualitative and quantitative results.

- Qualitative results are reported positive, negative, indeterminate, or borderline.
- Quantitative results are reported as numerical values that include a response to the TB antigen and two controls, nil and mitogen.
- Quantitative results may be useful for clinical decision making in individual cases, in combination with risk factors.

[a]For 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.

[b]Risk of TB for patients treated with corticosteroids increases with higher dose and longer duration.

AIDS, acquired immunodeficiency syndrome; TST, tuberculin skin tests.

Data 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. M.M.W.R. 1995;44(No. RR-11):19–34.

The Mantoux test is a quantitative TB skin test that uses tuberculin PPD. The standard 5-tuberculin-unit PPD dose is placed intracutaneously on the volar aspect of the forearm with a 26- or 27-gauge needle.[25,26] 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 135-1 lists the criteria for interpretation.[25,26] The Centers for Disease Control and Prevention (CDC) does not recommend the routine use of anergy panels.[25–28] Aplisol and tubersol 5-tuberculin-unit products are available commercially and are similar in sensitivity, specificity, and reactivity. It is important, however, to use one product and notify appropriate users when switching between products.[28]

The "booster effect" occurs for persons who do not respond to an initial skin test but show a positive reaction if retested about a week later or longer.[18,29] Persons with past *M. tuberculosis* infection and some with past immunization with bacillus Calmette-Guérin (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.[18,29] Once they are shown to be skin-test negative, any positive skin test later shows recent infection, and this requires an evaluation to consider treatment.

The PPD skin test is an imperfect diagnostic tool. Up to 20% of persons with active TB are falsely skin-test negative, presumably because they may be immunocompromised.[26,27] 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 especially if the induration is more than 15 mm.[25] These individuals require careful evaluation for active disease, and they may be offered preventive treatment because many come from areas where TB infection is common.

Interferon-*γ* release assays (IGRA) measure the release of INF-*γ* in blood in response to the TB antigens.[30] They may provide quick and specific results for identifying *M. tuberculosis*. IGRAs do not trigger a booster effect and are more specific for testing *M. tuberculosis* than the PPD. The QuantiFERON-TB Gold test is an enzyme-linked immunosorbent assay and the T-SPOT.®TB is an enzyme-linked immunospot assay.[30] Both tests can be used for diagnosing LTBI and TB disease caused by *M. tuberculosis*. However, these are the tests designed to diagnose LTBI and are not to be used to confirm or reject a diagnosis of active TB disease. For active TB, the IGRAs provide supporting evidence for the diagnosis but need to be interpreted in light of other evidence of active TB disease such as epidemiological risk factors and other studies. The antigenic proteins are absent from BCG vaccine strains and from most non-TB mycobacteria. Therefore, QuantiFERON-TB Gold test does not trigger a booster effect and is more specific for testing of *M. tuberculosis* than the PPD. Although these tests can provide results to diagnose both latent infection and disease, they cannot differentiate between the two. Results are available within 24 hours, instead of the 2 to 3 days required for the traditional PPD skin test; and the patient does not have to return to the clinic as required by the PPD skin test. The CDC has approved the use of these tests in all circumstances in which the PPD is used. IGRAs may be preferred for testing in patients who are suspected not to return for follow-up PPD reads or in patients who have received the BCG vaccine.[30] IGRA is recommended over a TST or PPD in individuals 5 years or older who meet the following criteria: (1) are likely to be infected with *M. tuberculosis*, (2) have a low-to-intermediate risk of disease progression, (3) testing for LTBI is warranted, (4) history of BCG vaccination, and (5) are unlikely to return to have their PPD read.[30] IGRA rather than PPD is also suggested in all other individuals who are likely to be infected with *M. tuberculosis*, who have a low-to-intermediate risk of disease progression, and in whom testing for LTBI is warranted.[30] There are insufficient data to recommend a preference for either a PPD or IGRA as the first-line diagnostic test in patients likely to be infected with *M. tuberculosis*, who have a high risk of progression to disease, and in whom diagnostic testing is warranted.[30] Figure 135-2 summarizes the recommendations for testing for latent tuberculosis infections (LTBI).

FIGURE 135-2

Summary of recommendations for testing for latent tuberculosis infection (LTBI).

Group	Testing Strategy	Considerations
Likely to Be Infected **High** Risk of Progression (TST ≥5 mM)	**Adults** **Acceptable:** IGRA or TST Consider dual testing where a positive result from either result would be considered **positive** **Children ≤5 years of age** **Acceptable:** TST **Acceptable:** IGRA or TST Consider dual testing where a positive result from either result would be considered **positive**[a]	Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns
Likely to Be Infected **Low** to **Intermediate** Risk of Progression (TST ≥10 mM)	**Preferred:** IGRA where available **Acceptable:** IGRA or TST	
Unlikely to Be Infected (TST >15 mM)	**Testing for LTBI is not recommended** **If necessary:** **Preferred:** IGRA where available **Acceptable:** Either IGRA OR TST **For serial testing:** **Acceptable:** Either IGRA OR TST Consider repeat or dual testing where a negative result from either would be considered **negative**[b]	

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

[a]Performing a second diagnostic test when the initial test is a negative is a strategy to increase sensitivity. This may reduce specificity, but the panel decided that this is an acceptable trade off in situations in which the consequences of missing LTBI exceed the consequences of inappropriate therapy. [b]Performing a confirmatory test following an initial positive result is based upon both the evidence that false positive results

are common among individuals who are unlikely to be infected with *Mycobacterium tuberculosis* and the committee's presumption that performing a second test on those patients whose initial test was positive will help identify initial false positive results. *(Adapted from Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. 2017;64:e1–e11.)*

The sensitivity for young children (younger than 5 years) and in immunocompromised individuals has not been clearly established.[31–33] A PPD test is recommended in healthy children (younger than 5 years) for whom diagnostic testing is warranted. The American Academy of Pediatrics recommends IGRAs in place of PPD skin test in immunocompetent children aged 5 years or older who have received BCG vaccination to confirm TB infection.[32] However, an increasing number of experts are using the IGRAs in children 3 years or older.

IGRAs perform similarly to the PPD in detecting TB in HIV-infected persons with LTBI. Both PPD and IGRA have suboptimal sensitivity for active TB especially in the severely immunocompromised.[34,35]

Culture and Staining

When active TB is suspected, attempts should be made to isolate *M. tuberculosis* from the site of infection.[18,25] Sputum collected in the morning usually has the highest yield.[18,25] Daily sputum collection over three consecutive days is recommended. Microscopic examination is the most rapid and inexpensive TB diagnostic tool. After staining, microscopic examination ("smear") detects about 8,000 to 10,000 organisms per milliliter (8×10^6/L to 10×10^6/L) of specimen, so a patient can be "smear-negative" but still grow *M. tuberculosis* on culture. Microscopic examination also cannot determine which of the more than 150 mycobacterial species is present or whether the organisms in the original samples were alive or dead.[18,25]

For persons unable to expectorate, sputum induction with aerosolized hypertonic saline may produce a diagnostic sample. Bronchoscopy, in older children, or aspiration of gastric fluid via a nasogastric tube, in children (5 years or younger), may be attempted for select individuals.[18] For persons 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 persons with acquired immunodeficiency syndrome (AIDS).[18,20]

Patient Care Process for Active Tuberculosis

Collect

- Patient characteristics (eg, age, sex, ethnicity)
- Patient medical history (medical risk factors, eg, immunocompromised, HIV, tobacco/ethanol/IV drug use)
- Social history (eg, living conditions, recent contacts)
- Current medications including prescription and nonprescription medicines, herbal products
- Information and history about patients adherence to medications

- History of clinical signs and symptoms (weight loss, cough, hemoptysis)
- Objective data
  - Sputum smears/culture
  - Chest x-ray
  - Tuberculin skin test (TST)/IGRA
  - Pertinent labs (white blood cell, platelets, serum creatinine, LFTs)

Assess

- Patient's potential for risk of transmission
- Risk of mycobacterial resistance
- Risk of drug malabsorption/drug interactions
- Need for therapeutic drug monitoring
- Immune status
- Ability/willingness to be adherent to prescribed regimen
- Psychological status to determine understanding and following instructions for adherence; need for directly observed therapy
- Ability/willingness to maintain follow-up

Plan*

- Devise a drug-therapy regimen with healthcare team to include most appropriate antituberculosis agents, dose, route, frequency, and duration (see Tables 135-3 and 135-4)
- Monitoring parameters including efficacy (eg, sputum smears) and safety (eg, LFTs, neuropathy); frequency and timing of follow-up (see Table 135-8)
- Patient education (eg, purpose of treatment, infection control, drug-specific information, importance of compliance/legal ramifications and risk of noncompliance)

Implement

- Provide patient education regarding all elements of treatment plan and goals
- Ensure patient understanding of risk of transmission and importance of adherence
- Schedule follow-up (eg, adherence assessment, adverse effects, response to treatment)

Follow-up: Monitor and Evaluate

- Monthly clinic evaluation
- Objective data
  - Sputum smears

- Chest x-ray results
- Pertinent labs

- Determine response to therapy
  - Clinical response (cough, fever, night sweats)
  - Culture results
- Need for therapeutic drug monitoring
- Presence of adverse effects
- Patient adherence to treatment plan
  - Tablet/Capsule counts for compliance or attending directly observed treatment

Collaborate with patients, caregivers, and other healthcare professionals.

TREATMENT

Drugs used in the treatment of active disease are divided into first-line and second-line agents. First-line agents should be the preferred options unless susceptibility results dictate otherwise. Treatment in special populations is also addressed.

Desired Outcome

The primary desired outcomes during the treatment of TB are:

1. Rapid identification of a new TB case.
2. Initiation of specific antituberculosis treatment.
3. Eradication of *M. tuberculosis* infection.
4. Achievement of a noninfectious state in the patient, thus ending isolation.
5. Prevention of the development of resistance.
6. Adherence to the treatment regimen by the patient.
7. Cure of the patient as quickly as possible (generally at least 6 months of treatment).

Patients with active disease should be isolated to prevent spread of the disease, and appropriate samples for smears and cultures should be collected. Secondary goals are identification of the index case that infected the individual, 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

Drug treatment is the cornerstone of TB management.[36] Monotherapy can be used only for infected persons who do not have active TB (latent infection, as shown by a positive skin test or positive IGRA). Once active disease is present, most patients receive four drugs.[36] The duration of treatment depends on the condition of the host, extent of disease, presence of drug resistance, and tolerance of medications. Most patients are treated for 6 months, and 18 to 24 months of treatment may be necessary for cases of MDR-TB.[36] Because the duration of treatment is so long and because many individuals feel better after a few weeks of treatment, careful follow-up is required. Directly observed therapy (DOT) by a healthcare

worker is a cost-effective way to ensure completion of treatment and is considered the standard of care.[37,38]

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.[15] As the number of organisms increases, the likelihood of naturally occurring drug-resistant mutants also increases. Naturally occurring mutants that are resistant to antituberculosis drugs are found at rates of 1 in 10^6 to 1 in 10^8 organisms.[14] When treating asymptomatic latent infection with monotherapy, the risk of selecting out resistant organisms is low. In contrast, the risk of selecting out isoniazid-resistant organisms is unacceptably high for 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).[14,36] It is unlikely that such rare organisms are present in a previously untreated patient.

Combination chemotherapy is required for treating active TB disease. Generally, four drugs are given at the outset of treatment. Of the most commonly used four drugs, rifampin and isoniazid are the best drugs for preventing resistance.[39]

Three subpopulations of mycobacteria are proposed to exist within the body, and each appears to respond to certain drugs.[36,39] Most numerous are the extracellular, rapidly dividing bacteria, often found within cavities (about 10^7-10^9 so-called "log phase" organisms). These are killed most readily by isoniazid, followed by rifampin.[39,40] A second group resides within caseating granulomas (possibly 10^5-10^7 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 so-called "acid phase" organisms. The third subset is the intracellular mycobacteria present within macrophages (10^4-10^6) and other "non-replicating persisters."[40] Rifampin, bedaquiline, and pretomanid appear to be most active against these "nonreplicating" persisters. While this model explains what happens during the treatment of TB, there is no practical way to quantitate these mycobacterial subpopulations within a given patient.

Nonpharmacologic Therapy

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) infected person 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.[29] 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 persons infected with TB 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 persons infected with TB. Surgery may be needed to remove destroyed lung tissue, space-occupying infected lesions (*tuberculomas*), and certain extrapulmonary lesions.[25] BCG is the only clinically relevant vaccine for TB in use today. Although it is one of the most commonly administered vaccines in history, it is of limited value, and cannot prevent infection by *M. tuberculosis.* BCG (discussed further) may prevent extreme forms of TB in infants.[25]

Pharmacologic Therapy

Treating Latent Infection

The treatment of LTBI has been called *prophylaxis.* The keys to successful treatment of LTBI are: (a) infection by a drug-susceptible isolate, (b) adherence to the regimen, and (c) no exogenous reinfection.[41] Table 135-2 lists the first-line treatment options for latent tuberculosis.

TABLE 135-2

Doses Recommended for Latent Tuberculosis Treatment Regimens

Drug	Duration	Dose
Isoniazid and rifapentine	Once weekly for 3 months	Adults and children ≥12 years: Isoniazid: 15 mg/kg Rifapentine: 10-14 kg: 300 mg 14.1-25 kg: 450 mg 25.1-32 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50 kg: 900 mg Children 2-11 years: Isoniazid: 25 mg/kg Rifapentine: see above
Isoniazid and rifampin	Daily for 3 months	Adult: Isoniazid: 5 mg/kg Rifampin: 10 mg/kg Children: Isoniazid: 10-20 mg/kg Rifampin: 15-20 mg/kg
Rifampin	Daily for 4 months	Adults: 10 mg/kg Children: 15-20 mg/kg

Data from Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69:1.

Because young children, older adults, and HIV-positive persons 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.[41]

There are three recommended treatment regimens for LTBI: 3 months of once-weekly isoniazid plus rifapentine; 4 months of daily rifampin or 3 months of daily isoniazid plus rifampin. Table 135-2 outlines recommended starting doses. The CDC recommends the 12-week isoniazid/rifapentine regimen as an equal alternative to 9 months of daily isoniazid for treating LTBI in otherwise healthy patients aged 12 years or older who have a predictive factor for a greater likelihood of developing active TB. These include recent exposure to contagious TB, conversion from negative to positive on an indirect test for infection (ie, IGRA or TST), radiographic findings of healed pulmonary TB, and untreated HIV infection.[41] Twelve weeks of once-weekly isoniazid and rifapentine by DOT was compared with daily self-administered isoniazid for 9 months in over 8,000 participants.[42] The isoniazid and rifapentine regimen was not inferior in efficacy to self-administered isoniazid, had a significantly higher completion rate (82% vs. 69%), and was associated with fewer grade 3 or 4 adverse reactions (1.6% vs. 3%).[42,43] Hypersensitivity reactions were more common with the isoniazid/rifapentine regimen and close clinical follow-up should be undertaken. These regimens are effective and safe.[43] The disadvantages of rifamycin-based regimens are the drug interactions. Rifabutin has less pronounced interactions than rifampin and may be used in place of rifampin due to contraindications or drug interactions. HIV-infected patients who are otherwise healthy and are not taking antiretroviral medications are also included in this category. The 3-month rifapentine and isoniazid combination is recommended for HIV-positive persons providing drug interactions allow.[41] Drug interactions with

rifapentine vary with the frequency of the dose and the affected companion drug. Precautions should be taken as HIV-infected patients are more likely to have extrapulmonary TB or pulmonary TB with normal findings on chest radiograph.

Alternative options for treatment of LTBI include 6 or 9 months of isoniazid which carry a higher toxicity risk and lower treatment completion rates due to the longer length of therapy.[41] For recent skin-test converters of all ages, the risk of active TB outweighs the risk for drug toxicity.[41] Pregnant females, persons who misuse alcohol, and those 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 neuropathies. All patients who receive treatment of LTBI should be monitored monthly for adverse drug reactions and for possible progression to active TB. Newer regimens under investigation include 1 month of daily rifapentine plus isoniazid (tested in HIV-positive patients to date), and 6 weeks of rifapentine daily alone. When resistance to isoniazid and rifampin is suspected in the isolate causing infection, there are no randomized controlled trials to prove what regimen should be used to treat LTBI among contacts.[41]

Treating Active Disease

8 The treatment of active TB requires the use of multiple drugs. There are two primary antituberculosis drugs, isoniazid and rifampin.[37,39] Isoniazid and rifampin should be used together whenever possible. Typically, *M. tuberculosis* is either susceptible or resistant to a given drug. Theoretically, minimal inhibitory concentration results could be used to guide dosing in the treatment of moderately resistant *M. tuberculosis*, but this remains to be studied prospectively.[37,39]

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.[5,36] 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.[5,36]

Drug resistance should be expected for 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.[36] A treatment history, often called a *drug-o-gram*, shows the start and stop dates of all antimycobacterial drugs on a horizontal bar graph.[36] A drug-o-gram should be constructed for all retreatment patients.

9 The standard TB treatment regimen is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months, a total of 6 months of treatment.[36] If susceptibility to isoniazid, rifampin, and pyrazinamide is shown, ethambutol can be stopped. Without pyrazinamide, a total of 9 months of isoniazid and rifampin treatment is required. Table 135-3 shows the recommended treatment regimens for drug susceptible tuberculosis. When intermittent therapy is used, DOT is essential. Doses missed during an intermittent TB regimen decrease its efficacy and increase the relapse rate. 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.[36]

TABLE 135-3

Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug Susceptible Organisms

Initial Phase			Continuation Phase		
Regimen	Drugs	Interval and Doses[a]	Drugs	Interval and Doses[a]	Comments[b,c]
1	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily for 8 weeks 7 days/week for 56 doses or 5 days/week for 40 doses[d]	Isoniazid/Rifampin	7 days/week for 126 doses or 5 days/week for 90 doses	This is preferred regimen for patient with newly diagnosed pulmonary tuberculosis.
2	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily for 8 weeks 7 days/week for 56 doses or 5 days/week for 40 doses[d]	Isoniazid/Rifampin	Three times weekly for 54 doses	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.
3	Isoniazid Rifampin Pyrazinamide Ethambutol	Three times weekly for 8 weeks Three times weekly for 24 doses	Isoniazid/Rifampin	Three times weekly for 54 doses	Caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.
4	Isoniazid Rifampin Ethambutol Pyrazinamide	Daily for 2 weeks, then twice weekly for 6 weeks 7 days/week for 14 doses, then twice weekly for 12 doses[e]	Isoniazid/Rifampin	Twice weekly for 36 doses	Do not use twice weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.
5	Rifapentine[f] Moxifloxacin Isoniazid Pyrazinamide	7days/week for 56 doses (8 weeks)	Rifapentine/Moxifloxacin	7days/week for 63 doses (9 weeks)	CDC interim guidance update to 2016 guidelines treatment option for U.S. patients aged ≥12 years with drug-susceptible pulmonary TB.

RIF, rifampin.

[a]When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days/week.

[b]Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

[c]Pyridoxine (vitamin B6), 25 to 50 mg/day, is given with isoniazid to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

[d]Five-day-a-week administration is always given by DOT.

[e]Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days/week for 15 doses (3 weeks), then twice weekly for 12 dose.

[f]High dose rifapentine 1200mg with food

Reprinted, with permission, from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 1 October 2016;63(7):853–867.

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.[36,44] 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.[36,44] Some authors recommend therapeutic drug monitoring (TDM), the use of serum drug concentrations, to optimize therapy for such patients.[40,45,46] When isoniazid and rifampin cannot be used, treatment durations often become 2 years or more regardless of immune status.[36,44] The most promising shorter regimens for MDR-TB may be the combination of bedaquiline, pretomanid and linezolid, generally for 6 months.[47] The treatment of MDR-TB will continue to evolve.

10 Adjustments to the regimen should be made once the susceptibility data are available.[36] 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.[5,36] In the United States, there is no standard regimen for MDR-TB.[5,36,47] Each patient's exposure history, 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 never add a single drug to a failing regimen.*[39,40] Adding one drug at a time leads to the sequential selection of drug resistance until there are no drugs left. TB specialists should be consulted regarding cases of MDR-TB. 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.[36,46] Consequently, prolonged respiratory isolation may be required.

Drug resistance should be considered in the following situations:

1. Patients who have received prior therapy for TB.
2. Patients from areas with a high prevalence of resistance (South Africa, Dominican Republic, Peru, Southeast Asia, the Baltic countries, and the former Soviet states).
3. Patients who are unhoused, institutionalized, or use IV drugs, … or who are infected with HIV.
4. Patients who still have AFB-positive sputum smears after 1 to 2 months of therapy.
5. Patients who still have positive cultures after 2 to 4 months of therapy.
6. Patients who fail treatment or relapse after treatment.
7. Patients known to be exposed to MDR-TB cases.

Empirical therapy with four or more drugs may be needed for acutely ill patients.[36] 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, with help from specialists. *XDR-TB* refers to "extensively drug-resistant TB." Such organisms are resistant to at least isoniazid, rifampin, a fluoroquinolone, and either bedaquiline or linezolid; refer such cases to specialists.[48,49]

Special Populations

Tuberculous Meningitis and Extrapulmonary Disease

Patients with CNS TB usually are treated for longer periods (9-12 months instead of 6 months).[36] In general, isoniazid, pyrazinamide, ethionamide, cycloserine, and linezolid penetrate the cerebrospinal fluid readily, but rifampin, ethambutol, and amikacin have variable CNS penetration.[40] Of the quinolones, levofloxacin may be preferred. Extrapulmonary TB of the soft tissues can be treated with conventional regimens.[36] TB of the bone typically is treated for 9 months, occasionally with surgical debridement.[36]

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.[36] Pediatric doses of isoniazid and rifampin on a milligram-per-kilogram basis are higher than those used in adults (Table 135-4).[36]

TABLE 135-4

Suggested Starting Doses[a] of First-Line Antituberculosis Drugs for Adults and Children[b,c]

Drug	Preparation	Adults/Children	Typical Doses			
			Daily	1× Per Week	2× Per Week	3× Per Week
First-Line Drugs						
Isoniazid	Tablets (50, 100, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for IV or intramuscular injection	Adults[c]	5 mg/kg	15 mg/kg	15 mg/kg	15 mg/kg
		Children[c]	10-15 mg/kg	—	20-30 mg/kg	—
Rifampin	Capsule (150, 300 mg); powder may be suspended for oral administration; aqueous solution for IV injection	Adults[d,e]	10 mg/kg	—	10 mg/kg	10 mg/kg
		Children[c]	10-20 mg/kg	—	10-20 mg/kg	—
Rifabutin	Capsule (150 mg)	Adult[d,e]	5 mg/kg	—	—	—
		Children	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults[c]	20 mg per kg daily is now being used for active TB	—	—	—
		Children	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	The drug is not approved for use in children

Pyrazinamide	Tablet (500 mg, scored)	Adults[c]	Weight 40-55 kg: 1,000 mg	—	Weight 40-55 kg: 2,000 mg	Weight 40-55 kg: 1,500 mg
			Weight 56-75 kg: 1,500 mg	—	Weight 56-75 kg: 3,000 mg	Weight 56-75 kg: 2,500 mg
			Weight 76-90 kg: 2,000 mg	—	Weight 76-90 kg: 4,000 mg	Weight 76-90 kg: 3,000 mg
		Children[c]	15-30 mg/kg	—	50 mg/kg	—
Ethambutol	Tablet (100, 400 mg)	Adults[c]	Weight 40-55 kg: 800 mg	—	Weight 40-55 kg: 2,000 mg	Weight 40-55 kg: 1,200 mg
			Weight 56-75 kg: 1,200 mg	—	Weight 56-75 kg: 2,800 mg	Weight 56-75 kg: 2,000 mg
			Weight 76-90 kg: 1,600 mg	—	Weight 76-90 kg: 4,000 mg	Weight 76-90 kg: 2,400 mg
		Children[d,e]	15-20 mg/kg daily	—	50 mg/kg	—

Higher doses of rifampin and rifapentine are being studied. Rifabutin dose may need to be adjusted when there is concomitant use of protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

[a]Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

[b]For purposes of this document, adult dosing begins at age 15 years.

[c]The authors of this chapter do not agree with the use of maximum doses, since this arbitrarily caps doses for patients who otherwise might need larger doses. These maximum doses were not based on prospective studies in large or overweight individuals, and do not consider patients with documented malabsorption of their medications. Clinical judgment should be used in such circumstances.

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

[e]It 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.

Data from Reference 37.

Pregnancy

Females 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.[50] Isoniazid and ethambutol are relatively safe for use in pregnant females.[50] B vitamins are particularly important during pregnancy and should be provided to females being treated for TB. Rifampin is associated rarely with birth defects, including limb reduction and CNS lesions.[36,50] In general, rifampin is used in pregnant females with TB. Pyrazinamide has not been studied in large numbers of pregnant women, but anecdotal data suggest that it may be safe.[36]

Aminoglycoside use during pregnancy may lead to hearing loss in the newborn, including complete deafness. Aminoglycosides must be reserved for critical situations where alternatives do not exist.[36] 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.[36,50] Down syndrome 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.[50] 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.[50]

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.[50] Although these drugs do not frequently cause joint problems in humans, other antituberculosis agents should be used during pregnancy.

Pregnant females with LTBI are not at the same level of risk compared with those with active disease. Therapy for LTBI may be delayed until after pregnancy. However, in the case of recent infection documented by a skin-test conversion or a newly positive IGRA and in immunosuppressed females who are found to have LTBI while pregnant, treatment for LTBI is started during the second trimester of pregnancy.[41,50] 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.[51]

HIV Infection

For drug-susceptible strains of tuberculosis, 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 135-3).[24,36] 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. Rifamycin-based treatments are most effective; however, agents should be selected based on susceptibility and HIV drug interactions. Prognosis has been particularly poor for HIV-infected patients infected with MDR-TB, so all efforts should be made to reduce the time between clinical presentation, diagnosis of TB, and start of appropriate treatment. Recommendations for management of HIV and TB published by the World Health Organization (WHO) and others have provided guidance on monitoring of treatment, side effects, and drug interactions of HIV and TB, MDR, and XDR-TB.[24,52] The timing for antiretroviral treatment in patients with TB and HIV is unclear. In patients with CD4 cell counts <200/mm^3 (0.20 × 10^9/L) or <50/mm^3 (0.05 × 10^9/L) reductions in mortality have been seen when antiretroviral treatment was initiated within 2 weeks of antituberculosis treatment.[52,53] Differentiation must be made between infection with *M. tuberculosis* and nontuberculous mycobacteria, such as *M. avium* complex, 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 in the “Therapeutic Drug Monitoring” section below.[45]

Renal Failure

For nearly all patients, isoniazid and rifampin do not require dose modification in renal failure. They are eliminated primarily by the liver.[40] 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 135-5).[36,40]

TABLE 135-5

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 (0.50 mL/s)[a,b,c,d]
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[e]
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)

[a]Standard doses are given unless there is intolerance.

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

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

[d]Data 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.

[e]The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity.

Reprinted, with permission, from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 1 October 2016;63(7):853–867.

Renally cleared TB drugs include the aminoglycosides (amikacin, kanamycin, and streptomycin), capreomycin, ethambutol, cycloserine, and levofloxacin.[36,40,54] Dosing intervals need to be extended for these drugs (Table 135-5). Moxifloxacin is 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.[36,54] *p*-Aminosalicylic acid is converted largely to metabolites prior to renal elimination; these metabolites may accumulate in renal failure.[54,55] 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.[55] Data regarding peritoneal dialysis are lacking. Ethambutol should be avoided in peritoneal dialysis patients, based on anecdotal evidence.

Hepatic Failure

Antituberculosis drugs that rely on hepatic clearance for most of their elimination include isoniazid, rifampin, pyrazinamide, ethionamide, and *p*-aminosalicylic acid.[40] Moxifloxacin is 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.[36,39,40] For some patients with drug-susceptible TB, a "liver-sparing" regimen may include linezolid, amikacin, levofloxacin, or ethambutol, at least temporarily.[36,39,40] 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 for patients with morbid obesity.[40] Relatively hydrophilic drugs (isoniazid, pyrazinamide, the aminoglycosides, capreomycin, *p*-aminosalicylic acid, and cycloserine) can be dosed initially based on ideal body weight. Low or high serum concentrations can be avoided by checking the serum concentrations.[45]

The TB Drugs

The interested reader is referred to several other publications for more detailed information regarding these drugs (see Table 135-4).[36,44,45] The "maximum" dose for a given patient is the dose that produces the desired response with an acceptable level of toxicity.[45] 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 minimal inhibitory concentration against *M. tuberculosis* of 0.01 to 0.25 mcg/mL (mg/L; 0.07-1.82 µmol/L). It is bactericidal and is thought to inhibit mycolic acid synthesis and disruption of the cell wall in susceptible organisms.[56] Most nontuberculous mycobacteria such as *M. avium* are resistant to isoniazid, although *M. kansasii* and *M. xenopi* are susceptible. The most common mechanisms of resistance result from mutations in the *katG* or *inhA* genes.[56]

Isoniazid is readily absorbed from the GI tract and from intramuscular injection sites. It also can be given as a short IV infusion over 5 minutes if diluted in about 20 mL of normal saline.[57] Isoniazid should be given on an empty stomach whenever possible.[57] *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 Native Alaskans 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.[56] Poor absorption and rapid clearance of isoniazid for patients receiving highly intermittent therapy are associated with poor clinical outcomes.[56,58]

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.[36] Overt hepatotoxicity, however, occurs in only 1% of cases. Risk factors for hepatotoxicity include patient age, preexisting liver disease, excessive alcohol intake, pregnancy, coadministration of other medications that are potentially hepatotoxic, 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 females, persons who misuse alcohol, children, and the malnourished, are at increased risk. Isoniazid may inhibit the metabolism of phenytoin, carbamazepine, primidone, and warfarin.[39] 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 (6-9 months).[36] 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*.[59] It is also 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.[36,59]

Rifampin usually is given orally, but it also can be given as a 30-minute IV infusion.[59] Oral doses are best given on an empty stomach.[60] Patients with AIDS, diabetes, and other GI problems have difficulty absorbing rifampin after oral doses, and this has been associated with therapeutic failures in some cases.[36,59,61] Rifampin is metabolized to 25-desacetyl rifampin, which retains some 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.[40,45] Higher doses (1,200-2,400 mg) are being considered based on clinical trials.[62]

Elevations in hepatic enzymes have been attributed to rifampin in 10% to 15% of patients, with overt hepatotoxicity occurring in less than 1%.[36,59] More frequent adverse effects of rifampin include rash, fever, and GI 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 take the form of a flu-like syndrome with development of fever, chills, headache, arthralgias, and, rarely, hypotension and shock.[37] 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 135-6). HIV-positive patients may benefit from the use of rifabutin instead of rifampin.[24,36,60] Furthermore, 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. Rifampin may turn urine and other secretions orange-red and may permanently stain some types of contact lenses.

TABLE 135-6

Recommended Regimens for the Concomitant Treatment of TB and HIV Infection in Adults

Combined Regimen for Treatment of HIV and TB	Pharmacokinetic Effect of the Rifamycin	Tolerability/Toxicity	Antiviral Activity When Used with Rifamycin	Recommendations (Comments)
Efavirenz-based antiretroviral therapy[a] with rifampin-based TB treatment	Well-characterized, modest decrease in concentrations in some patients	Low rates of discontinuation	Excellent	Preferred (efavirenz should not be used during the first trimester of pregnancy)
PI-based antiretroviral therapy[a] with rifabutin-based TB treatment	Little effect of rifabutin on PI concentrations, but marked increases in	Low rates of discontinuation (if rifabutin is appropriately dose-reduced)	Favorable, although published clinical experience is not extensive	Preferred for patients unable to take efavirenz[b] (caution to ensure patients who discontinue PI not to continue to receive reduced rifabutin dose)

	rifabutin concentrations			
Nevirapine-based antiretroviral therapy with rifampin-based TB treatment	Moderate decrease in concentrations	Concern about hepatotoxicity when used with isoniazid, rifampin, and pyrazinamide	Suboptimal when nevirapine is initiated using once-daily dosing largely favorable when nevirapine is given twice daily throughout cotreatment	Alternative for patients who cannot take efavirenz, though efavirenz is preferred (nevirapine should not be initiated among women with CD4 > 250 cells/μL [0.25 × 10^9/L] or men with CD4 > 400 cells/μL [0.40 ×10^9/L])
Raltegravir-based antiretroviral therapy with rifampin-based TB treatment	Significant decrease in concentrations with standard dosing	Limited experience	Limited published clinical experience	Alternative at higher doses for patients who cannot take efavirenz and who have baseline viral load <100,000 copies/mL (100 × 10^6/L)
Dolutegravir-based antiretroviral therapy with rifampin-based TB-treatment	Coadministration with rifampicin results in decreases in dolutegravir plasma exposure requiring increased dose of dolutegravir	Limited experience	Limited published clinical experience	Alternative for patients who cannot take efavirenz
Zidovudine/lamivudine/abacavir/tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	No published clinical experience, but this regimen is less effective than efavirenz- or atazanavir-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz or nevirapine and if rifabutin not available
Zidovudine/lamivudine/tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, no other effects predicted	Anemia	Favorable, but not evaluated in a randomized trial	Alternative for patients who cannot take efavirenz and abacavir and if rifabutin not available
Zidovudine/lamivudine/abacavir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz- or nevirapine-based	Alternative for patients who cannot take efavirenz and tenofovir and if rifabutin not available

			regimens in persons not taking rifampin	
Superboosted[c] lopinavir-based antiretroviral therapy or double dose lopinavir/ritonavir-based therapy with rifampin-based TB treatment	Moderate decrease in concentrations	Hepatitis	Early favorable experience of super-boosting among young children and double dose among adults already on antiretroviral drugs at the time of rifampin initiation	Alternative if rifabutin not available; double dose an option among adults already taking lopinavir-based antiretroviral therapy and virologically suppressed at the time of tuberculosis treatment initiation; super boosting has not been adequately tested in adults but may be effective

[a]With two nucleoside analogues.

[b]Includes patients with NNRTI-resistant HIV, those unable to tolerate efavirenz, and women during the first one to two trimesters of pregnancy.

[c]Super boosting of lopinavir is achieved by giving lopinavir 400 mg together with 400 mg ritonavir twice daily. Double dose lopinavir/ritonavir is lopinavir 800 mg plus ritonavir 200 mg twice daily.

Data from Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. 2013. Available at: https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations02.htm.

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 for patients who are receiving HIV protease inhibitors.[37,50,61,62] For HIV-positive patients, the American Thoracic Society/CDC recommends regimens with three or more doses of the TB drugs per week (see Table 135-3). Rifapentine is a long-acting rifamycin that has been tested as part of a 4-month regimen that includes moxifloxacin for selected TB patients.[63] It is approximately as potent an enzyme inducer as rifampin, so similar drug interactions are likely.[52,64]

Pyrazinamide

Adding pyrazinamide to the first 2 months of treatment with isoniazid and rifampin shortens the duration to 6 months for most patients.[36] Pyrazinamide may be bacteriostatic or bactericidal depending on the concentration and the susceptibility of the organism. It is usually well absorbed and displays a fairly long half-life.[40,65] The most common toxicities of pyrazinamide are GI distress, arthralgias, and elevations in the serum uric acid concentrations.[36,44] 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) 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 DOT, 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.[40] It is used as a fourth drug for TB while awaiting susceptibility data and its use is intended to prevent emergence of rifampin resistance.[36,44] If the organism is susceptible to isoniazid, rifampin, and pyrazinamide, ethambutol can be stopped. Ethambutol is active against most mycobacteria, by inhibiting synthesis of metabolites and impairing cell metabolism, and is generally bacteriostatic.

Ethambutol should not be given with antacids.[66,67] For patients with renal failure, the ethambutol dose should be reduced to three times per week.[68] 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.[36]

Quinolones

Levofloxacin and moxifloxacin are sometimes used to treat MDR-TB because of their excellent activity against *M. tuberculosis*. Table 135-7 lists WHO proposed categories of drugs for treating MDR-TB and XDR-TB. Moxifloxacin is a possible replacement for certain first-line agents.[69,70] Moxifloxacin has been compared with isoniazid and ethambutol during the first 8 weeks of therapy for pulmonary TB. There was no significant increase in 8-week culture negativity when compared with isoniazid. However, shorter time to culture conversion was seen when compared with ethambutol.[70] A 4-month regimen consisting of moxifloxacin, rifapentine, isoniazid, and pyrazinamide was compared with a similar 4-month regimen that included ethambutol in place of moxifloxacin, or to the standard 6-month regimen of rifampin, isoniazid, pyrazinamide, and ethambutol. The daily 4-month regimen that included moxifloxacin was as effective as the standard daily 6-month regimen. The CDC issued an interim guidance that recommends the 4-month regimen of moxifloxacin, rifapentine, isoniazid, and pyrazinamide as a treatment option for U.S. persons aged > 12 years with drug-susceptible pulmonary tuberculosis.[71,72] Quinolones are useful because most are available in oral and IV dosage forms, so they can be used in critically ill patients. However, resistance of MTB to the fluoroquinolones is a major concern. Resistance is attributed to mutations in the gyrA and gyrB genes and can develop in a relatively short period of time.[59,73]

TABLE 135-7

The WHO Proposed Categories of Drugs for Treating MDR- and XDR-TB[a]

Groups and steps	Medicine
Group A: Include all three medicines	Levofloxacin or moxifloxacin
	Bedaquiline[b,c]
	Linezolid[d]
Group B: Add one or both medicines	Clofazimine
	Cycloserine or terizidone
	Ethambutol
	Delamanid[d]
	Pyrazinamide[f]
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Imipenem–cilastatin or meropenem[g]
	Amikacin (or streptomycin)[h]
	Ethionamide orprothionamide[i]
	P-aminosalicylic acidi

ECG: electrocardiogram; GDG: Guideline Development Group; IPD: individual patient data; LPA: line probe assay.

[a]This table is intended to guide the design of individualized, longer MDR-TB regimens medicines in Group C are ranked by decreasing order of usual preference for use, subject to other considerations.

[b]*Adapted from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 1 October 2016;63(7):853–867.*

[c]In 2019, new evidence on the concurrent use of bedaquiline and delamanid was made available to the GDG. With regard to safety, the GDG concluded that the data suggest no additional safety concerns regarding concurrent use of bedaquiline and delamanid. Both medicines may be used concurrently in patients who have limited other treatment options available to them, provided that sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place. The data on the effectiveness of concurrent use of bedaquiline and delamanid were reviewed by the GDG, but owing to the limited evidence and potential residual confounding in the data, the GDG was unable to proceed with a recommendation on effectiveness.

[d]Use of linezolid for at least 6 months has been shown to increase effectiveness, although toxicity may limit use.

[e]Evidence on the safety and effectiveness of delamanid beyond 6 months and in children aged under 3 years was insufficient for review. The use of delamanid beyond these limits should follow best practices in “off-label” use.

[f]Pyrazinamide is counted as an effective agent only when confirmed susceptibility.

[g]Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

[h]Amikacin and streptomycin are to be considered only when confirmed susceptibility, and if high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used and confirmed susceptibility (ie, resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic drug-susceptibility testing is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

[i]These agents showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine, or delamanid, and are thus proposed only when other options to compose a regimen are not possible.

Bedaquiline

Bedaquiline is a diarylquinoline that operates by a new mechanism which targets the ATP synthase pump and depletes cellular energy stores and does not demonstrate cross-resistance with existing TB drugs.[74,75] The WHO and CDC have issued recommendations stating that bedaquiline may be used at a dose of 400 mg daily for 2 weeks and then 200 mg three times a week for 22 weeks of treatment in adults with pulmonary MDR-TB when an effective treatment regimen cannot otherwise be provided.[76] Bedaquiline may be used on a case-by-case basis in children, HIV-infected persons, pregnant females, and in individuals with extrapulmonary TB. Patients treated with bedaquiline should be closely monitored every week for potential side effects and an electrocardiogram (QT monitoring) should be performed at baseline and at weeks 2, 12, and 24.[73,76] The QT monitoring is required due to a black box warning issued by the FDA as a result of increased rates of death due to QT prolongation in patients receiving bedaquiline.[74,75]

Linezolid

Linezolid is a synthetic inhibitor of ribosomal translation that has been used for drug-resistant Gram-positive infections since 2000.[73] It has oral bioavailability near 100% that is not affected by food.[73,77] Clearance involves oxidation of the morpholine ring, and renal elimination of parent drug plus metabolites.[59,73,77] CSF concentrations are 57% of plasma.[77] The most frequently used dose for TB is 600 mg once daily. Higher doses appear to be more toxic.[36,76,78] Trough concentrations are associated with mitochondrial toxicity, leading to cytopenias and peripheral and ocular neuropathies.[73] Rifampin can reduce linezolid plasma exposure by about a third.[73] Linezolid is a weak inhibitor of monoamine oxidase and should usually not be used with MAOIs, SSRIs or triptans due to reports of serotonergic syndrome.[77]

Clofazimine

Clofazimine is a drug with good activity against *M. leprae* and some activity against *M. tuberculosis* and *M. avium*. It is used in doses of 100 mg daily in advanced cases of MDR-TB or *M. avium* complex, especially when therapeutic options are limited.[36,40] The drug has a terminal elimination half-life that is weeks long. GI distress and skin discoloration are the most important adverse reactions. Although uncommon, severe GI pain may occur because of deposition of clofazimine crystals within the intestines; this may require surgical correction.[77]

Delamanid and Pretomanid

Delamanid and Pretomanid are nitroimidazole derivatives that are chemically related to metronidazole and work through inhibiting mycolic acid synthesis.[77,79] These agents have potent in vitro and in vivo activity with low minimal inhibitory concentrations against *M. tuberculosis*.[80] Delamanid has centralized marketing authorization by the European Medicines Agency for use in the European Union.[80] Pretomanid is FDA-approved as part of a regimen including bedaquiline and linezolid, the so-called BPaL regimen. Food increases pretomanid absorption.[75,81] Pretomanid is metabolized by multiple reductive and oxidative pathways, with CYP3A4 responsible for approximately 20%.[70] Efavirenz reduces the AUC of pretomanid by 35%, and rifampin reduces the AUC by 66%.[75,81] Combinations of pretomanid with other antituberculosis drugs are also being investigated.

Beta-lactams: Imipenem, Meropenem, and Ceftazidime

Imipenem and meropenem are synthetic carbapenems, and ceftazidime is a third-generation cephalosporin.[59,77] These antibiotics target penicillin-binding proteins which are involved in bacterial cell-wall synthesis.[59,77] Resistance occurs by enzymatic degradation. Specifically, *M. tuberculosis* possesses an extended spectrum class A β-lactamase (BlaC), which must be inactivated.[77] Clavulanic acid and avibactam are beta-lactamase inhibitors

that prevent the enzymatic degradation caused by β-lactamase.[59,77,82] Clavulanic acid can be given orally (only in combination with amoxicillin); the other drugs are given intravenously.[73] Dosing has been empiric, and has not been established. Imipenem has been dosed at 1,000 mg 12 hours and meropenem at 1,000 mg 8 hours, intravenously.

Aminoglycosides

Streptomycin, amikacin, and kanamycin are active against mycobacteria, and amikacin is preferred for TB. Aminoglycosides are given IM or IV and are renally cleared by glomerular filtration. They must be dosed appropriately in patients with renal dysfunction.[45,81]

Aminoglycosides occasionally cause nephrotoxicity, although it tends to be mild and reversible. They also cause ototoxicity (vestibular and cochlear), which may become permanent with continued use.[59,81] Older patients and those receiving long durations of treatment are most likely to experience hearing loss, whereas vestibular toxicity is highly unpredictable.[59]

Ethionamide

Ethionamide shares structural features with two other antimycobacterial agents, isoniazid and 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.[40,59] GI 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 GI intolerance. Food does not affect absorption significantly.[83] Little ethionamide is recovered in the urine, so doses remain the same in renal failure.[55] Ethionamide may cause goiter with or without hypothyroidism (especially when given with p-aminosalicylic acid), gynecomastia, alopecia, impotence, menorrhagia, and photodermatitis. The management of diabetes also may be more difficult for patients receiving ethionamide. Because of these problems, ethionamide only is used when necessary.

p-Aminosalicylic Acid

In the United States, only the enteric-coated, sustained-release granule form (Paser) is available.[40,84] GI 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 also is 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.[85,86]

Various types of malabsorption, including steatorrhea, were reported with previous dosage forms of *p*-aminosalicylic acid. Hypersensitivity and, rarely, severe hepatitis may occur. *p*-Aminosalicylic acid is known to produce goiter, with or without myxedema, which seems to occur more frequently with concomitant ethionamide therapy.[40,59]

Other New Drugs and Delivery Systems

Other new drugs in Phase II trials for treatment of TB include: Delpazolid (LCB01-0371) and sutezolid (PNU-100480) that target protein synthesis. SQ-109 is a new chemical class that targets MmpL3, an essential membrane transporter involved in the building of the mycolic acids as part of the outer membrane of mycobacteria. Macozinone (PBTZ-169) targets the flavoenzyme DprE1, blocking the synthesis of the cell wall precursor decaprenyl phosphoarabinose and provoking lysis of the *M. tuberculosis.* Liposomes are under investigation as delivery systems for various agents against mycobacteria, including isoniazid, rifampin, and the aminoglycosides. By changing the pharmacokinetic profile of such agents, their use in the treatment of mycobacterial infections could be enhanced greatly.

Corticosteroids

Adjunctive therapy with corticosteroids may be of benefit for some patients with tuberculous meningitis or pericarditis to relieve inflammation and pressure.[36] They should be avoided in most other circumstances because they detract from the immune response to TB.

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 TST.

The efficacy of several different BCG preparations ranged from negative 56% (some patients did worse with the vaccine) to positive 80%.[37,87] The primary benefit of BCG vaccination appears to be the prevention of severe forms of TB in children.[88] The incidence of tuberculous meningitis and miliary TB is 52% to 100% lower and incidence of pulmonary TB is 2% to 80% lower in vaccinated children younger than 15 years than it was in unvaccinated controls.[88,89]

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. Pregnant women and patients with impaired immune systems, including those with HIV infection, should avoid vaccination. The WHO had 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.[36]

THERAPEUTIC DRUG MONITORING

TDM, or applied pharmacokinetics, generally should be used if patients are failing appropriate treatment (no clinical improvement after 2-4 weeks or smear positive after 4-6 weeks).[45,81,90] Patients with AIDS, diabetes, obesity, cystic fibrosis, various GI disorders, or MDR-TB may be tested prospectively, before problems arise, to ensure adequate treatment. 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.[91,92] Finally, TDM of the TB and HIV drugs is perhaps the most logical way to untangle the complex drug interactions that take place.[52,93]

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of the Pharmaceutical Care Plan

The most serious problem with TB therapy is patient nonadherence to the prescribed regimens.[36] Unfortunately, there is no reliable way to identify such patients a priori. Noncompliance rates of up to 89% have been reported with TB therapy.[91,94] 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 DOT.[36] Despite criticisms that it will cost more money, DOT is far cheaper in the long run to prevent the further spread of disease with DOT than to track down and treat additional cases of TB continuously.

The homeless and other underprivileged individuals are often assumed to constitute a group of patients considered “unreliable,” and DOT should be reserved for them; it is also assumed that “responsible” patients cared for by private physicians may be treated with daily, unsupervised therapy. However, outcomes (sputum culture conversion to negative at 3 months) for patients with pulmonary TB who were treated by private physicians were compared with outcomes for patients treated via DOT in a city-run clinic. Three-month culture conversion occurred in only 40% of the private-care patients, compared with 90% in the city clinic-care patients.[91,94] Clearly, expansion of the use of DOT to nearly all patients with TB may be of benefit.

Patients who are AFB-smear positive should have sputum samples sent for AFB stains every 1 to 2 weeks until two consecutive smears are negative. This provides early evidence of a response to treatment.[36] 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 (eg, advanced age, alcohol abuse, pregnancy)[36] (Table 135-8). Hepatotoxicity should be suspected for patients whose serum transaminases

exceed five times the upper limit of normal or whose total bilirubin concentration exceeds 3 mg/dL (51.3 µmol/L) and for patients with symptoms such as nausea, vomiting, or jaundice. At this point, the offending agent(s) should be discontinued. Sequential reintroduction 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 for patients who must receive aminoglycosides 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.

TABLE 135-8

Antituberculosis Drug Monitoring Table

Drug	Adverse Effects	Monitoring
Isoniazid	Asymptomatic elevation of aminotransferases, clinical hepatitis, fatal hepatitis, peripheral neurotoxicity, CNS effects, lupus-like syndrome, hypersensitivity, monoamine poisoning, diarrhea	LFT monthly in patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of drug; dosage adjustments may be necessary in patients receiving anticonvulsants or warfarin
Rifampin	Cutaneous reactions, GI reactions (nausea, anorexia, abdominal pain), flu-like syndrome, hepatotoxicity, severe immunologic reactions, orange discoloration of bodily fluids (sputum, urine, sweat, tears), drug interactions due to induction of hepatic microsomal enzymes	Liver enzymes and interacting drugs as needed (eg, warfarin)
Rifabutin	Hematologic toxicity, uveitis, GI symptoms, polyarthralgias, hepatotoxicity, pseudojaundice (skin discoloration with normal bilirubin), rash, flu-like syndrome, orange discoloration of bodily fluids (sputum, urine, sweat, tears)	Drug interactions are less problematic than rifampin
Rifapentine	Similar to those associated with rifampin	Drug interactions are being investigated and are likely similar to rifampin
Pyrazinamide	Hepatotoxicity, GI symptoms (nausea, vomiting), nongouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis, transient morbilliform rash, dermatitis	Serum uric acid can serve as a surrogate marker for adherence; LFTs in patients with underlying liver disease
Ethambutol	Retrobulbar neuritis, peripheral neuritis, cutaneous reactions	Baseline visual acuity testing and testing of color discrimination; monthly testing of visual acuity and color discrimination in patients taking >15-20 mg/kg, having renal insufficiency, or receiving the drug for >2 months
Streptomycin	Ototoxicity, neurotoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Amikacin/kanamycin	Ototoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr; monthly assessments of renal function and auditory or vestibular symptoms

Capreomycin	Nephrotoxicity, ototoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr Monthly assessments of renal function and auditory or vestibular symptoms Baseline and monthly serum K^+ and Mg^{2+}
p-Aminosalicylic acid	Hepatotoxicity, GI distress, malabsorption syndrome, hypothyroidism, coagulopathy	Baseline LFTs and TSH TSH every 3 months
Moxifloxacin	GI disturbance, neurologic effects, cutaneous reactions	No specific monitoring recommended
Bedaquililne	GI disturbances, dizziness, headache, rash, arthralgia	Serum K, Ca, MgECG at baseline, weeks 2, 12, 24. Weekly ECG for persons taking other QTc prolonging drugs, history of arrhythmias, hypothyroidism, uncompensated heart failure, or have serum K, Ca, or Mg below normal

LFT, liver function test; SCr, serum creatinine; TSH, thyroid-stimulating hormone.

Data from Nahid P, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 1 October 2016;63(7):853–867.

ABBREVIATIONS

AFB	acid-fast bacillus
BCG	bacillus Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
DOT	directly observed treatment
DTH	delayed-type hypersensitivity
HIV	human immunodeficiency virus
IGRA	interferon-γ release assay
IL	interleukin
INF	interferon
LAM	lipoarabinomannan
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MDR	multidrug-resistant
PPD	purified protein derivative
TB	tuberculosis
TDM	therapeutic drug monitoring
TH_1	T-helper type 1
TH_2	T-helper type 2
TNF	tumor necrosis factor
TST	tuberculin skin test
WHO	World Health Organization
XDR	extensively drug-resistant

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SELF-ASSESSMENT QUESTIONS

1. A 42-year-old man is receiving treatment for pulmonary TB. He has received 9 weeks of daily rifampin, isoniazid, ethambutol, and pyrazinamide. His sputum smear and cultures have been negative. Susceptibility results have just been made available and indicate the isolate is resistant to isoniazid. Which of the following would be the most appropriate recommendation for your patient at this time?

   A. Discontinue isoniazid, continue rifampin, pyrazinamide, and ethambutol × 6 months.

   B. Discontinue isoniazid, continue rifampin, pyrazinamide, ethambutol, and add levofloxacin × 4 months.

   C. Discontinue isoniazid and ethambutol, continue rifampin and pyrazinamide × 4 months.

   D. Discontinue isoniazid, pyrazinamide and ethambutol, continue rifampin × 4 months.

2. TC is a 74-year-old-man recently diagnosed with multidrug-resistant (MDR)-TB. His physician is thinking about starting a regimen of amikacin, levofloxacin, cycloserine, and *p*-aminosalicylic acid, but is uncertain if this is correct. Therefore, he asks you to evaluate this proposed regimen. You note that his susceptibility tests indicate his organism is susceptible to: amikacin, ethambutol, levofloxacin, cycloserine, and *p*-aminosalicylic acid. His estimated creatinine clearance is 25 mL/min (0.42 mL/s); he has a history of psychosis. From this information, you recommend the following:

   A. Replace the planned cycloserine with ethambutol; make adjustments to amikacin for renal dysfunction.

   B. Continue the planned regimen, but make adjustments to amikacin for renal dysfunction.

   C. Replace *p*-aminosalicylic acid with ethambutol; make adjustments to amikacin for renal dysfunction.

   D. Treat with levofloxacin, cycloserine, and *p*-aminosalicylic acid.

3. Which one of the following patients presenting with cough, fever, and weight loss would be at greatest risk of having TB disease?

   A. Joe who recently travelled to a resort in Cancun, Mexico

   B. Emily who volunteers on holidays at a homeless shelter

   C. Brian who works at a Vietnamese restaurant

   D. Lisa who is on infliximab for rheumatoid arthritis

4. SL has been on antituberculosis treatment for 2 months, which of the following tests would be most appropriate to determine her response to

therapy?

A. Mantoux test

B. Nucleic acid amplification test

C. Acid fast baccili (AFB) culture

D. Interferon Gamma release assay (QuantiFERON®TB Gold)

5. After being discharged from the hospital, LB comes to your pharmacy with prescriptions to continue her antituberculosis regimen. Which of the following drugs would cause pruritus and orange discoloration of her urine, sputum, sweat, and tears?

A. Isoniazid

B. Ethambutol

C. Rifampin

D. Pyrazinamide

6. A 68-year-old Asian male with active TB has been on a four-drug antituberculosis medication (rifampin, isoniazid, pyrazinamide, and ethambutol) regimen for 5 weeks. He complains that his right big toe has been painful for 2 weeks, and recently, he has a hard time walking around the house. On examination, the right big toe is tender and red. Laboratory testing shows an elevated uric acid level and gout is suspected. Which of the following antituberculosis medications is most likely associated with this side effect?

A. Isoniazid

B. Pyrazinamide

C. Rifampin

D. Ethambutol

7. An otherwise healthy 29-year-old Asian female with active TB has been improving symptomatically after 6 weeks of antituberculosis medications (rifampin, isoniazid, pyrazinamide, and ethambutol). However, for the past 2 weeks, she has noticed trouble reading phone numbers in the phonebook, and has had trouble reading the newspaper.

On examination, her visual acuity and red/green perception are diminished. The most likely diagnosis is:

A. Ethambutol-associated optic neuritis

B. Isoniazid-induced hepatitis

C. Macular degeneration

D. TB dissemination to her eyes

8. BC is a 36-year-old patient severely immunocompromised with human immunodeficiency virus (HIV) and TB coinfection. Which of the following is the most appropriate treatment approach in this patient?

A. Defer antiretroviral therapy until after TB treatment.

B. Start antiretroviral therapy and then treat start TB treatment 4 weeks later.

C. Start TB therapy and then start antiretroviral therapy as soon as possible after.

D. Start both antiretroviral therapy and TB treatment together, as soon as possible.

9. A 55-year-old emergency room nurse was exposed to TB 4 weeks ago. Susceptibility data are pending for the patient's isolate. Her current purified protein derivative (PPD) was read as 8 mm induration. She has no symptoms and her chest x-ray is normal. Which of the following is the best option in this patient?

   A. No treatment needed at this time because the patient is asymptomatic

   B. Rifampin daily for 12 months

   C. Isoniazid daily for 9 months

   D. Rifampin and pyrazinamide for 4 months

10. Which of the following regimens would be the best option for a 26-year-old pregnant female recently diagnosed with active TB?

   A. Isoniazid, rifampin, and pyrazinamide

   B. Isoniazid, rifampin, and ethambutol

   C. Isoniazid, ethambutol, and pyrazinamide

   D. Isoniazid, rifampin, and streptomycin

11. A 67-year-old man has received 8 weeks of therapy with rifampin, isoniazid, ethambutol, and pyrazinamide. His sputum was negative for AFB within 2 weeks of initiating therapy. Laboratory tests are drawn and liver function tests are reported as: AST 166 IU/L (8-48 IU/L) and ALT 96 IU/L (7-55 IU/L) (or AST 2.77 µkat/L [0.13-0.80 µkat/L] and ALT 1.60 µkat/L [0.12-0.92 µkat/L]). Which of the following would be the best option for the patient at this time?

   A. Discontinue isoniazid and rifampin and start pyrazinamide, levofloxacin, and ethionamide.

   B. Discontinue isoniazid and rifampin and add moxifloxacin and check serum concentrations of his TB drugs.

   C. Discontinue all TB drugs, continue to recheck liver function tests, and restart same treatment when liver function returns to normal.

   D. Continue current treatment and continue to monitor for continued elevation of liver function tests.

12. A 23-year-old Hispanic male with HIV infection and active TB is receiving highly active antiretroviral therapy and antituberculous treatment with rifabutin, isoniazid, pyrazinamide, and ethambutol by directly observed treatment (DOT). He reports that his right eye has been hurting him for 3 days and is now red. What is the most likely medication for TB, when she has been on four-drug antituberculosis-induced condition?

   A. Ethambutol-induced optic neuritis

   B. Isoniazid-induced peripheral neuropathy

   C. Pyrazinamide-induced acidosis leading to optic neuritis

   D. Rifabutin-related uveitis

13. Which of the following regimens is not an option for treatment of latent TB infection?

   A. Rifampin daily × 4 months

   B. Isoniazid and rifapentine DOT once weekly × 3 months

   C. Isoniazid and rifampin daily for 6 months

D. Isoniazid DOT twice weekly for 6 months

14. TS is a 58-year-old woman with drug-susceptible TB. She has been on four-drug antituberculosis treatment for 6 weeks and is still smear positive. Which of the following options below would be the most appropriate to do at this time?

    A. Add streptomycin to her regimen and check serum concentrations of her TB drugs.

    B. Continue treatment; *M. tuberculosis* is slow growing and 6 weeks is not enough time to convert to smear-negative.

    C. Inform the patient that her treatment will need to be extended to 12 months.

    D. Continue current treatment and check serum concentrations of her TB drugs.

15. Rifabutin should be chosen over rifapentine or rifampin when a patient is on certain combined antiretroviral combinations because it:

    A. Has a better side effect profile in HIV-positive patients.

    B. Is less likely to induce hepatic clearance of the antiretroviral drugs.

    C. It has a lower risk of uveitis.

    D. Serum concentration monitoring is available for rifabutin.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Isoniazid is the only drug that should be discontinued. It is not necessary to add additional agents because smear and cultures are negative and the patient is responding. Therapy should continue with the remaining drugs for at least 6 months.

2. **A.** In patients with creatinine clearance estimated to be less than 30 mL/min (0.5 mL/s), pyrazinamide and ethambutol are recommended to be administered three times per week rather than daily.

3. **D.** While all of these patients would have some increased risk, immunocompromised patients including those on TNF-alpha inhibitors are at high risk for reactivation of latent TB.

4. **C.** Response to therapy and continuation is guided by the sputum and AFB culture results at 2 months and the presence of cavitary disease on chest X-ray at the time of treatment initiation.

5. **C.** Patients on rifampin will typically see orange discoloration of body fluids which may stain clothes and contacts. Other common side effects with rifampin include: pruritus, flu like syndrome, nausea/diarrhea, headache, hematologic effects, and elevated liver function tests.

6. **B.** Pyrazinamide often increases serum uric acid levels. Serum uric acid may be obtained in patients with history of gout especially in the setting of renal insufficiency or with the use of medications which decrease uric acid secretion.

7. **A.** Optic neuropathy is an important side effect of ethambutol that should be monitored especially at higher doses. Patients on ethambutol noting changes in their vision should be referred to an ophthalmologist.

8. **C.** Severely immunocompromised HIV patients with pulmonary tuberculosis should be started on a tuberculosis treatment regimen and antiretroviral treatment should be initiated as soon as possible to reduce the risk of death and risk of immune reconstitution inflammatory syndrome.

9. **C.** The patient was exposed to an active TB patient recently. Her PPD would be considered positive because she was in close contact with an active contagious case in addition to a positive T-Spot test. Since the isolate was resistant to rifamycin, the best option for this patient would be isoniazid for 9 months.

10. **B.** Untreated tuberculosis disease presents a higher risk to the mother and fetus than treatment. The regimen of choice for empiric treatment of

presumed drug-susceptible active TB during pregnancy in the United States consists of isoniazid, rifampin, and ethambutol administered for 2 months followed by isoniazid and rifampin for 7 months, for a total of 9 months of therapy

11. **D.** Transient elevations in liver function tests may occur during the first few week of treatment with isoniazid and rifampin. If liver function tests continue to escalate beyond five times the upper limit of normal, discontinuation should be considered.

12. **D.** Cycloserine should be avoided in patients with a history of seizure disorder and used with caution in patients with preexisting mental health issues since it is associated with neuropsychiatric adverse reactions.

13. **C.** Rifampin-based regimens are now preferred as they are shorter in duration and provide excellent tolerability and efficacy. As an alternative regimen, isoniazid can be administered daily for 6 or 9 months as treatment for latent tuberculosis.

14. **D.** Positive sputum cultures after 3 months of antituberculosis therapy requires a review of causes for treatment failure including susceptibility testing and serum concentrations. Additional agents should be added, never add a single drug to a failing regimen.

15. **B.** Rifamycins induce hepatic CYP3A4 enzymes that can accelerate metabolism of protease inhibitors and some nonnucleoside reverse transcriptase inhibitors. Rifabutin is a less potent inducer than rifampin. As rifabutin is also a substrate for CYP3A4 it may require dose adjustments depending on the coadministered drugs.