Chapter 50: Tuberculosis

INTRODUCTION

- *Tuberculosis* (TB) is a communicable infectious disease caused by *Mycobacterium tuberculosis*. It can produce silent, latent infection, as well as progressive, active disease. Globally, 2 billion people are infected and roughly 1.5 million people die from TB each year.

PATHOPHYSIOLOGY AND ETIOLOGY

- *M. tuberculosis* is transmitted from person to person by coughing or other activities that cause the organism to be aerosolized. Close contacts of TB patients are most likely to become infected.
- Human immunodeficiency virus (HIV) is the most important risk factor for progressing to active TB, especially among people 25–44 years of age. An HIV-infected individual with TB infection is over 100-fold more likely to develop active disease than an HIV-seronegative patient.
- Approximately 90% of patients who experience primary disease have no further clinical manifestations other than a positive skin test either alone or in combination with radiographic evidence of stable granulomas. Tissue necrosis and calcification of the originally infected site and regional lymph nodes may occur, resulting in the formation of a radiodense area referred to as a *Ghon complex*.
- Approximately 5% of patients (usually children, the elderly, or the immunocompromised) experience progressive primary disease at the site of the primary infection (usually the lower lobes) and frequently by dissemination, leading to meningitis and often to involvement of the upper lobes of the lung as well.
- Approximately 10% of patients develop reactivation disease, which arises subsequent to the hematogenous spread of the organism. In the United States, most cases of TB are believed to result from reactivation.
- Occasionally, a massive inoculum of organisms may be introduced into the bloodstream, causing widely disseminated disease and granuloma formation known as *miliary TB*.

CLINICAL PRESENTATION AND DIAGNOSIS

- Patients with TB typically present with cough, weight loss, fatigue, fever, and night sweats. Symptom onset may be gradual.
- Frank hemoptysis usually occurs late in the course of disease but may present earlier.
- On physical examination, the patient is usually thin with evidence or recent weight loss. Dullness to chest percussion, rales, and increased vocal fremitus are often present, but a normal lung examination is common compared to the degree of radiological lung involvement.
- The white blood cell (WBC) count is usually moderately elevated with lymphocyte predominance. A high platelet count (thrombocytosis) and mild-to-moderate anemia are common.
- Sputum smear is done to detect mycobacteria. A fiber-optic bronchoscopy is performed if sputum tests are inconclusive and suspicion is high.
- Chest radiograph shows patchy or nodular infiltrates in the apical areas of the upper lobes or the superior segment of the lower lobes. There may be cavitation that shows air–fluid levels as the infection progresses.
- Clinical features associated with extrapulmonary TB vary depending on the organ system(s) involved but typically consist of slowly progressive decline of organ function with low-grade fever and other constitutional symptoms.

- Patients with HIV may have atypical presentation. HIV-positive patients are less likely to have positive skin tests, cavitary lesions, or fever. They have a higher incidence of extrapulmonary TB and are more likely to present with progressive primary disease.
- TB in older persons is easily confused with other respiratory diseases. It is far less likely to present with positive skin tests, fevers, night sweats, sputum production, or hemoptysis. TB in children may present as typical bacterial pneumonia and is called *progressive primary TB.*
- The most widely used screening method for tuberculous infection is the tuberculin skin test, which uses purified protein derivative (PPD). Populations most likely to benefit from skin testing are listed in **Table 50-1**. Testing for latent TB is summarized in **Figure 50-1**.
- The Mantoux method of PPD administration consists of the intracutaneous injection of PPD containing five tuberculin units. The test is read 48–72 hours after injection by measuring the diameter of the zone of induration.
- Some patients may exhibit a positive test 1 week after an initial negative test; this is referred to as a *booster effect.*
- Confirmatory diagnosis of a clinical suspicion of TB must be made via chest radiograph and microbiologic examination of sputum or other infected material to rule out active disease.
- When active TB is suspected, attempts should be made to isolate *M. tuberculosis* from the infected site. Daily sputum collection over 3 consecutive days is recommended.
- Tests to measure release of interferon-γ in the patient's blood in response to TB antigens may provide quick and specific results for identifying *M. tuberculosis.*

FIGURE 50-1

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

Performing A Second Diagnostic Test When The Initial Test Is A Negative Is A Strategy To Increase Sensitivity. This May Reduce Specifically, 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. 2Performing 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 Jamil SM, et al. Diagnosis of tuberculosis in adults and children. Ann Am Thorac. 2017;14(2):275–278.)

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**[1]	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**[2]	

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 50-1

Criteria for Tuberculosis Positivity

Reaction ≥5 mm of induration	Reaction ≥10 mm of induration	Reaction ≥15 mm of induration
HIV-infected persons	Recent immigrants (ie, within the last 5 years) from high-prevalence countries	Persons with no risk factors for TB
A recent contact of a person with TB disease	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	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	
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]	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	

Interpretation of Interferon Gamma Release Assay (IGRA) Results

The interpretation of IGRAs is based on the amount of IFN-γ, in T-SPOT®.TB. An IGRA is recommended over a tuberculin skin test (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 latent tuberculosis infection (LTBI) testing is necessary; and who have been vaccinated against Calmette-Guerin 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; HIV, human immunodeficiency virus; TB, tuberculosis.

Source: 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.

- Goals of Treatment: (1) Rapid identification of a new TB case; (2) Initiation of specific anti-TB treatment; (3) Eradicating *M. tuberculosis* infection; (4) Achievement of a noninfectious state in the patient, thus ending isolation; (5) Preventing the development of resistance; (6) Adherence to the treatment regimen by the patient; and (7) Cure of the patient as quickly as possible (generally at least 6 months of treatment).
- Drug treatment is the cornerstone of TB management. A minimum of two drugs, and generally three or four drugs, must be used simultaneously. 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.
- Drug treatment is continued for at least 6 months, and 18–24 months for cases of multidrug-resistant TB (MDR-TB).
- Debilitated patients may require therapy for other medical conditions, including substance abuse and HIV infection, and some may need nutritional support.
- Surgery may be needed to remove destroyed lung tissue, space-occupying lesions, and some extrapulmonary lesions.

PHARMACOLOGIC THERAPY

Latent Infection

- As described in **Table 50-2**, chemoprophylaxis should be initiated in patients to reduce the risk of progression to active disease.
- **Isoniazid**, 300 mg (5–10 mg/kg of body weight) daily in adults, is the preferred treatment for latent TB in the United States, generally given for 9 months.
- **Rifampin**, 600 mg daily for 4 months, can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid. **Rifabutin**, 300 mg daily, may be substituted for rifampin for patients at high risk of drug interactions.
- The CDC recommends the 12-week **isoniazid/rifapentine** regimen as an equal alternative to 9 months of daily isoniazid for treating latent tuberculosis infection (LTBI) in otherwise healthy patients aged 12 years or older who have a predictive factor for greater likelihood of TB developing, which included recent exposure to contagious TB, conversion from negative to positive on an indirect test for infection (ie, interferon-gamma release assays [IGRA] or tuberculin skin test), and radiographic findings of healed pulmonary TB.
- Pregnant women, alcoholics, and patients with poor diets who are treated with isoniazid should receive pyridoxine, 10–50 mg daily, to reduce the incidence of central nervous system (CNS) effects or peripheral neuropathies.

TABLE 50-2

Choosing the Most Effective Treatment of LTBI

Drug	Duration	Dose	Frequency	Comments
Isoniazid	9 months	Adult: 5 mg/kg Children: 10–20 mg/kg[a]	Daily	In HIV-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-NRTIs (NNRTIs) Preferred regimen in children 2–11 years
	9 months	Adult: 15 mg/kg Children: 20–40 mg/kg[a]	Twice weekly[c]	Directly observed treatment (DOT) must be used with twice-weekly dosing
	6 months	Adult: 5 mg/kg Children: Not recommended	Daily	Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients
	6 months	Adult: 15 mg/kg Children: Not recommended	Twice weekly[c]	Directly observed treatment (DOT) must be used with twice-weekly dosing
Isoniazid and rifapentine	3 months	Rifapentine 10.0–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: 900 mg	Once weekly[c]	Equal alternative to 9 months of daily isoniazid for otherwise healthy patients age >12 years DOT is recommended Not recommended for children <2 years; HIV-infected patients taking antiretroviral therapy, presumed resistance, pregnant women or women expecting to become pregnant during the treatment period DOT must be used
Rifampin	4 months	Adult: 10 mg/kg Children: 15–20 mg/kg[b]	Daily	For persons who are contacts of patients with isoniazid-resistant rifampin-susceptible Can be considered for persons who cannot tolerate isoniazid or who have been exposed to isoniazid-resistant TB Rifampin should not be used to treat HIV-infected person taking some combinations of ART

[a]The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regiment and 20–30 mg/kg for twice-weekly regimen.

[b]In the United States, the recommended regimen for the treatment of LTBI in children is a 9-month course of isoniazid. For the treatment of LTBI in infants, children, and adolescents when isoniazid could not be tolerated or the child has had contact with a case patient infected with an isoniazid resistant but rifamycin susceptible organism, the American Academy of Pediatrics recommends 6 months of daily rifampin (180 doses) at a dosage of 10 mg/kg.

[c]Intermittent regimens must be provided via directly observed therapy (DOT), that is, healthcare worker observes the ingestion of medication.

Source: Adapted from Latent tuberculosis infection: A guide for primary health care providers. US Department of Health and Human Services/CDC. Atlanta, GA, 2013.

Treating Active Disease

- **Table 50-3** lists options for treatment of culture-positive pulmonary TB caused by drug-susceptible organisms. Doses of antituberculosis drugs are given in **Table 50-4**. Other sources should be consulted for treatment recommendations when TB is concurrent with HIV infection. The standard TB treatment regimen is **isoniazid, rifampin, pyrazinamide, and ethambutol** for 2 months, followed by isoniazid and rifampin for 4 months. Ethambutol can be stopped if susceptibility to isoniazid, rifampin, and pyrazinamide is shown.
- Appropriate samples should be sent for culture and susceptibility testing prior to initiating therapy for all patients with active TB. The data should guide the initial drug selection for the new patient. If susceptibility data are not available, the drug resistance pattern in the area where the patient likely acquired TB should be used.
- If the patient is being evaluated for the retreatment of TB, it is imperative to know what drugs were used previously and for how long.
- 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.
- Patients who are slow to respond, those who remain culture positive at 2 months of treatment, those with cavitary lesions on chest radiograph, and HIV-positive patients should be treated for 9 months and for at least 6 months from the time they convert to smear and culture negativity.

TABLE 50-3

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

Initial Phase			Continuation Phase		
Regimen	**Drugs[a]**	**Interval and Doses[b] (Minimal Duration)**	**Drugs**	**Interval and Doses[c] (Minimal Duration)**	**Comments[c,e]**
1	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)[c]	Isoniazid/Rifampin	7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)[c]	This is preferred regimen for patient with newly diagnosed pulmonary tuberculosis.
2	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 56 doses or 5 days/week for 40 doses (8 weeks)	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)[d]	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.
3	Isoniazid Rifampin Pyrazinamide Ethambutol	3 times weekly for 24 doses (8 weeks)	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)	Use regimen with 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	7 days/week for 14 doses, then twice weekly for 12 doses[e]	Isoniazid/Rifampin	Twice weekly for 36 doses (18 weeks)	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.

[a]Other combinations may be appropriate in certain circumstances.

[b]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.

[c]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.

[d]Pyridoxine (vitamin B_6), 25–50 mg/day, is given with INH 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.

[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 doses.

DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

Source: 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, Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, pp. 853–867.

TABLE 50-4

Antituberculosis Drugs for Adults and Children

Drug	Preparation	Adults/Children	Typical Doses[a]			
			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 Children	5 mg/kg 10–15 mg/kg	15 mg/kg —	15 mg/kg 20–30 mg/kg	15 mg/kg —
Rifampin[h]	Capsule (150, 300 mg); powder may be suspended for oral administration; aqueous solution for IV injection	Adults[b] Children	10 mg/kg 10–20 mg/kg	— —	10 mg/kg 10–20 mg/kg	10 mg/kg —
Rifabutin	Capsule (150 mg)	Adults[b] Children	5 mg/kg Appropriate dosing for children is unknown	—		5 mg/kg
Rifapentine[h]	Tablet (150 mg, film coated)	Adults Children	— The drug is not approved for use in children <12 years old	10–20 mg/kg (continuation phase)	—	—

Pyrazinamide	Tablet (500 mg, scored)	Adults Children	40–55 kg: 1000 mg 56–75 kg: 1500 mg 76–90 kg: 2000 mg 30–40 mg/kg	— — — —	40–55 kg: 2000 mg 56–75 kg: 3000 mg 76–90 kg: 4000 mg 50 mg/kg	40–55 kg: 1500 mg 56–75 kg: 2500 mg 76–90 kg: 3000 mg —
Ethambutol	Tablet (100, 400 mg)	Adults Children[b]	40–55 kg: 800 mg 56–75 kg: 1200 mg 76–90 kg: 1600 mg 30–40 mg/kg	— — — —	40–55 kg: 2000 mg 56–75 kg: 2800 mg 76–90 kg: 4000 mg —	40–55 kg: 1200 mg 56–75 kg: 2000 mg 76–90 kg: 2400 mg 50 mg/kg
Second-line drugs						
Cycloserine	Capsule (250 mg)	Adults Children	10–15 mg/kg/day, usually 500–750 mg/day in two doses[c] 10–15 mg/kg/day	No data —	No data —	No data —
Ethionamide	Tablet (250 mg)	Adults[d] Children	15–20 mg/kg/day, usually 500–750 mg/day in a single daily dose or two divided doses[f] 15–20 mg/kg/day	No data No data	No data No data	No data No data
Streptomycin	Aqueous solution (1-g vials) for IV or intramuscular administration	Adults Children[i]	15 mg/kg/day[e] 15–20 mg/kg/day	— —	— 25–30 mg/kg	— 25 mg/kg

Amikacin/Kanamycin	Aqueous solution (500-mg and 1-g vials) for IV or intramuscular administration	Adults Children[i]	15 mg/kg/day[e] 15–20 mg/kg/day IV or intramuscular as a single daily dose	— —	— 25–30 mg/kg	25 mg/kg —
Capreomycin	Aqueous solution (1-g vials) for IV or intramuscular administration	Adults Children[i]	15 mg/kg/day[g] 15–20 mg/kg/day as a single daily dose	e —	25–30 mg/kg	25 mg/kg 25–30 mg/kg
p-Aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food; tablets (500 mg) are still available in some countries, but not in the United States; a solution for IV administration is available in Europe	Adults Children	8–12 g/day in two or three doses 200–300 mg/kg/day in two to four divided doses	No data No data	No data No data	No data No data
Levofloxacin	Tablets (250, 500, 750 mg); aqueous solution (500-mg vials) for IV injection	Adults Children	500–1000 mg daily f	No data f	No data f	No data f
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for IV injection	Adults Children	400 mg daily g	No data g	No data g	No data g
Bedaquiline		Adults Children	Weeks 1–2: 400 mg daily. Weeks 3–24: 200 mg three times weekly. The drug is not approved for use in children	No data	No data	No data

[a]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.

[b]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.

[c]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.

[d]The single daily dose can be given at bedtime or with the main meal to reduce nausea.

[e]Dose: 15 mg/kg/day (1 g), and 10 mg/kg in persons older than 59 years (750 mg). Usual dose: 750–1000 mg administered intramuscularly or IV, given as a single dose 5–7 days/week and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

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

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

[h]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.

[i]Larger total body water content and faster clearance of injectable drugs in most children. Dosing can be guided by serum concentrations.

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

Source: 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, Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, pp. 853–867.

Drug Resistance

- If the organism is drug resistant, the aim is to introduce two or more active agents that the patient has not received previously. With MDR-TB, no standard regimen can be proposed. It is critical to avoid monotherapy or adding only a single drug to a failing regimen.
- Drug resistance should be suspected in the following situations:

  ✔ Patients who have received prior therapy for TB

  ✔ Patients from geographic areas with a high prevalence of resistance (South Africa, Mexico, Southeast Asia, the Baltic countries, and the former Soviet states)

  ✔ Patients who are homeless, institutionalized, IV drug abusers, and/or infected with HIV

  ✔ Patients who still have acid-fast bacilli–positive sputum smears after 2 months of therapy

  ✔ Patients who still have positive cultures after 2–4 months of therapy

  ✔ Patients who fail therapy or relapse after retreatment

  ✔ Patients known to be exposed to MDR-TB cases

Special Populations

Tuberculous Meningitis and Extrapulmonary Disease

- In general, **isoniazid, pyrazinamide, ethionamide**, and **cycloserine** penetrate the cerebrospinal fluid readily. Patients with CNS TB are often treated for longer periods (9–12 months). Extrapulmonary TB of the soft tissues can be treated with conventional regimens. TB of the bone is typically treated for 9 months, occasionally with surgical debridement.

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. Pediatric doses of drugs should be used.

Pregnant Women

- The usual treatment of pregnant women is **isoniazid, rifampin, and ethambutol** for 9 months.
- Women with TB should be cautioned against becoming pregnant, as the disease poses a risk to the fetus as well as to the mother. Isoniazid or ethambutol is relatively safe when used during pregnancy. Supplementation with B vitamins is particularly important during pregnancy. **Rifampin** has been rarely associated with birth defects, but those seen are occasionally severe, including limb reduction and CNS lesions. **Pyrazinamide** has not been studied in a large number of pregnant women, but anecdotal information suggests that it may be safe. **Ethionamide** may be associated with premature delivery, congenital deformities, and Down syndrome when used during pregnancy, so it cannot be recommended in pregnancy. **Streptomycin** has been associated with hearing impairment in the newborn, including complete deafness and must be reserved for critical situations where alternatives do not exist. **Cycloserine** is not recommended during pregnancy. Fluoroquinolones should be avoided in pregnancy and during nursing.

Renal Failure

- In nearly all patients, isoniazid and rifampin do not require dose modifications in renal failure. Pyrazinamide and ethambutol typically require a reduction in dosing frequency from daily to three times weekly (**Table 50-5**).

TABLE 50-5

Dosing Recommendations for Adults with Reduced Renal Function and for Adults Receiving Hemodialysis

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients with Creatinine Clearance <30 mL/min (0.50 mL/sec) or for Patients Receiving Hemodialysis[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	750–1000 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 currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing, using serum concentration monitoring.

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

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EVALUATION OF THERAPEUTIC OUTCOMES AND PATIENT MONITORIG

- The most serious problem with TB therapy is nonadherence to the prescribed regimen. The most effective way to ensure adherence is with DOT.
- Patients who are AFB smear positive should have sputum samples sent for acid-fast bacilli stains every 1–2 weeks until two consecutive smears are negative. Once on maintenance therapy, patients should have sputum cultures performed monthly until negative, which generally occurs over 2–3 months. If sputum cultures continue to be positive after 2 months, drug susceptibility testing should be repeated, and serum drug concentrations should be checked.
- Patients should have blood urea nitrogen, serum creatinine, aspartate transaminase or alanine transaminase, and a complete blood count determined at baseline and periodically, depending on the presence of other factors that may increase the likelihood of toxicity (advanced age, alcohol abuse, and possibly pregnancy). Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin exceeds 3 mg/dL (51.3 µmol/L). At this point, the offending agent(s) should be discontinued and alternatives selected.
- See **Table 50-6** for drug monitoring recommendations.

TABLE 50-6

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 rifabutin concentrations	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)
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 [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	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

	dosing			× 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 aatazanavir-based regimens in person 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 regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz and tenofovir and if rifabutin not available
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 superboosting 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; superboosting 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]Superboosting 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.

ART, antiretroviral therapy; HIV, human immunodeficiency virus; TB, tuberculosis.

Source: CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [online]. 2013. Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm.

See Chapter 130, Tuberculosis, authored by Rocsanna Namdar and Charles A. Peloquin, for a more detailed discussion of this topic.