

College of Pharmacy  
Fourth year. Clinical Pharmacy  
**Infectious Diseases**  
**Tuberculosis**

## **Introduction**

1-Tuberculosis (TB) is a **communicable infectious disease** caused by *Mycobacterium tuberculosis*. It can produce silent, **latent infection**, as well as progressive, **active disease**.

2-Globally, **2 billion people are infected** and roughly **1.5 million people die** from TB each year.

## **Pathophysiology and etiology**

1-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.

2-**Human immunodeficiency virus (HIV) is the most important risk factor** for progressing to active TB. An HIV-infected individual with TB infection is over **100-fold more likely** to develop active disease than an HIV-seronegative patient.

4-Approximately **90% of patients** who experience primary disease **have no further clinical manifestations**.

5-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.

6-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**

1-Patients with TB typically present with **cough, weight loss, fatigue, fever, and night sweats**. Symptom onset may be gradual.

2-Frank **hemoptysis** usually occurs late in the course of disease but may present earlier.

3-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.

4-**Sputum smear** is done to **detect mycobacteria**. **Chest radiograph** is also important.

5-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.

6-Patients with **HIV may have atypical presentation**. HIV-positive patients are **less likely to have positive skin tests, or fever**. They have a **higher incidence of extrapulmonary TB** and are more likely to present with **progressive primary disease**.

7-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.

8-TB in **children** may present as **typical bacterial pneumonia** and is called progressive primary TB.

9-The most widely used **screening method for tuberculous infection is the tuberculin skin test**, which uses purified protein derivative (PPD).

10-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.

11-Tests to measure release of **interferon- $\gamma$**  in the patient's blood in response to TB antigens may provide **quick and specific results for identifying M. tuberculosis**.

## **Treatment**

1-**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).

2-**Drug treatment is the cornerstone of TB management**. A minimum of **two drugs**, and **generally three or four drugs**, must be used **simultaneously**.

3-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.

4-Drug treatment is continued for **at least 6 months**, and **18–24 months for cases of multidrug-resistant TB (MDR-TB)**.

5-**Surgery may be needed** to remove destroyed lung tissue, space-occupying lesions, and some extrapulmonary lesions.

## **Pharmacologic Therapy**

### **Latent Infection**

1-Chemoprophylaxis should be initiated in patients **to reduce the risk of progression to active disease**.

2-**Isoniazid**, 300 mg daily in adults, is the preferred treatment for latent TB, **generally given for 9 months**.

3-**Rifampin**, **600 mg daily for 4 months**, can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid.

4-**Rifabutin**, 300 mg daily, may be substituted for rifampin for patients at high risk of drug interactions.

5-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**.

## Treating Active Disease

1-Table 1 lists options for treatment of culture-positive pulmonary TB caused by drug-susceptible organisms.

**Table 1: Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug Susceptible Organisms**

Initial Phase			Continuation Phase		
Regimen	Drugs <sup>a</sup>	Interval and Doses <sup>b</sup> (Minimal Duration)	Drugs	Interval and Doses <sup>c</sup> (Minimal Duration)	Comments <sup>c,e</sup>
1	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks) <sup>c</sup>	Isoniazid/Rifampin	7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks) <sup>c</sup>	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) <sup>d</sup>	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 <sup>e</sup>	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.

<sup>a</sup>Other combinations may be appropriate in certain circumstances.

<sup>b</sup>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.

<sup>c</sup>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.

<sup>d</sup>Pyridoxine (vitamin B6), 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.

<sup>e</sup>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.

2-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)**. Ethambutol can be stopped if susceptibility to isoniazid, rifampin, and pyrazinamide is shown.

3-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.

4-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.**

5-Patients who are slow to respond, those who remain culture positive at 2 months of treatment, those with cavitory 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.**

## **Drug Resistance**

1-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.

2-It is critical to **avoid monotherapy or adding only a single drug** to a failing regimen.

3-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**

1-In general, **isoniazid**, **pyrazinamide**, **ethionamide**, and **cycloserine** penetrate the cerebrospinal fluid readily.

2-Patients with **CNS TB** are often **treated for longer periods (9–12 months).**

3-**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**

1-TB in children may be treated with regimens similar to those used in adults, although some **physicians still prefer to extend treatment to 9 months.**

2-**Pediatric doses** of drugs should be used.

### **Pregnant Women**

1-The usual treatment of pregnant women is **isoniazid**, **rifampin**, and **ethambutol for 9 months.**

2-Women with TB should be **cautioned against becoming pregnant**, as the disease poses a risk to the fetus as well as to the mother.

**3-Isoniazid** or **ethambutol** is **relatively safe** when used during pregnancy. Supplementation **with B vitamins** is particularly important during pregnancy.

**4-Rifampin** has been **rarely associated with birth defects**, but those seen are occasionally severe, including limb reduction and CNS lesions.

**5-Pyrazinamide** has **not been studied in a large number of pregnant women**, but anecdotal information suggests that it may be safe.

**6-Ethionamide** may be associated with premature delivery, congenital deformities, and Down syndrome when used during pregnancy, so it cannot be recommended in pregnancy.

**7-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.

**8-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.**

## **Evaluation of therapeutic outcomes**

**1-The most serious problem with TB therapy is nonadherence** to the prescribed regimen. **The most effective way to ensure adherence is with DOT.**

**2-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.

**3-Once on maintenance therapy, patients should have sputum cultures performed monthly until negative, which generally occurs over 2–3 months.**

**4-If sputum cultures continue to be positive after 2 months,** drug susceptibility testing should be repeated, and serum drug concentrations should be checked.

**5-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).

**6-Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin exceeds 3 mg/dL.** At this point, the offending agent(s) should be discontinued and alternatives selected.

## **Reference**

**Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11<sup>th</sup> Edition. 2021.**