Tuberculosis (TB)

BY

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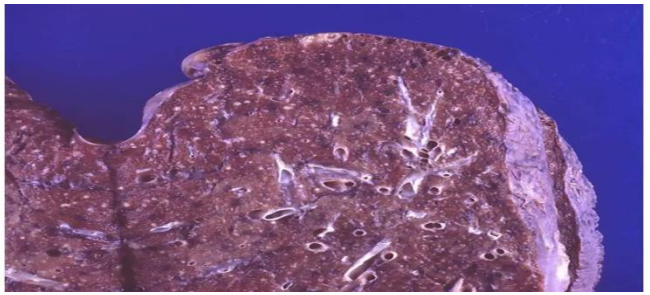
- **Tuberculosis** (TB) is a **communicable infectious disease** caused by *Mycobacterium tuberculosis*. It can produce silent, **latent infection**, as well as progressive, **active disease**

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. 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.**

- 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.

- Occasionally, **a massive inoculum of organisms may be introduced into the bloodstream**, causing widely disseminated disease and granuloma formation known as **miliary TB.**
- Miliary tuberculosis is **a potentially life-threatening type of tuberculosis that occurs when a large number of the bacteria travel through the bloodstream and spread throughout the body**



Clinical presentation

- 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.
- 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**. **Chest radiograph** is also important.

- 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, 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 s**creening method for tuberculous infection is the tuberculin skin test**, which uses purified protein derivative (PPD).
- 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**

Treatment

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

Pharmacologic Therapy
1.Latent Infection

- Chemoprophylaxis should be initiated in patients **to reduce the risk of progression to active disease.**
- **Isoniazid**, 300 mg daily in adults, is the preferred treatment for latent TB, **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.
- 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**.

2.Treating Active Disease

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.

- 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.
- 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 the patient is being evaluated for the retreatment of TB, **it is imperative to know what drugs were used previously and for how long.**
- 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.**

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.**

Evaluation of therapeutic outcomes

- **The most serious problem with TB therapy is nonadherence**
- Patients who are **AFB smear positive should have sputum samples sent for acid-fast bacilli stains every 1–2 weeks**
- 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 nitroge**n, serum **creatinine**, **aspartate transaminase** or **alanine transaminase**, and a **complete blood count**
- **Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin exceeds 3 mg/dL**