College of Pharmacy
Clinical Pharmacy

Infectious Diseases
Tuberculosis Lec:2

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 infecte**d 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.**

- **The number needed to treat (NNT)** is the number of patients who need a specific treatment to prevent one additional bad outcome (eg, myocardial infarction, stroke). he number needed to treat is the inverse of the absolute risk reduction (ARR). Example: if a drug reduces the risk of a bad outcome from 50% to 40%, the ARR = 0.5 - 0.4 = 0.1. Therefore, the NNT = 1/ARR = 10.

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- Both tests(PPD and IGRA) measure delayed-type hypersensitivity reaction or type IV cell-mediated immunity involving T-lymphocytes, which are activated after exposure to mycobacteria.
The most widely used s**creening method for tuberculous infection is the tuberculin skin test**, which uses purified protein derivative (PPD),Tuberculin skin test (TST) (Mantoux test).
a. Recommended dose is 5 tuberculin units/0.1 mL.
b. Mantoux method
i. Intradermal injection of tuberculin into forearm
ii. Measure diameter of induration after 48–72 hours. **Induration of 15 mm or more is considered positive**.
c. False-negative tests occur in 15%–20% of people infected with *M. tuberculosis*, primarily in those recently infected or anergic.
d. Only 8% of people vaccinated with bacille Calmette-Guérin (BCG) at birth will react 15 years later

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-γ** 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. Rifabutin has reduced potential for drug interactions (relative to rifampin) , Rifapentine has a longer half-life than rifampin.

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[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.

aOther combinations may be appropriate in certain circumstances.
bWhen 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.
cBased 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.
dPyridoxine (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.
eAlternatively, 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 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

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 nitroge**n, 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, 11th Edition. 2021.