Chemotherapy of Tuberculosis

Introduction

- Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*, which primarily affects the lungs but can also involve other organs (extrapulmonary TB).
- TB chemotherapy is essential not only for curing the disease but also for preventing transmission, relapse, and the emergence of drug resistance.
- **TB treatment requires multiple drugs administered over several months due to:**
  - The slow-growing nature of the bacteria
  - The presence of intracellular and dormant bacilli
  - Risk of drug resistance from monotherapy
- The standard approach is called DOTS (Directly Observed Treatment, Short-course), promoted by WHO.

Classification of Anti-Tubercular Drugs

A. First-Line Anti-TB Drugs (used in standard regimens):

Drug	Code	Type
Isoniazid	H	Bactericidal
Rifampicin	R	Bactericidal
Pyrazinamide	Z	Bactericidal (acidic pH)
Ethambutol	E	Bacteriostatic
Streptomycin	S	Bactericidal (extracellular)

B. Second-Line Anti-TB Drugs (used in resistant TB):

- **Fluoroquinolones**: Levofloxacin, Moxifloxacin
- **Injectables**: Amikacin, Capreomycin, Kanamycin
- **Others**: Ethionamide, Cycloserine, PAS (para-aminosalicylic acid), Bedaquiline, Linezolid, Delamanid

Mechanism of Action

Drug	Mechanism of Action
Isoniazid	Inhibits synthesis of mycolic acid (a component of mycobacterial cell wall)
Rifampicin	Inhibits DNA-dependent RNA polymerase, blocking transcription
Pyrazinamide	Converted to active form in acidic environment → disrupts membrane potential and energy production

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Ethambutol	Inhibits arabinosyl transferase → impairs cell wall synthesis (arabinogalactan)
Streptomycin	Binds to 30S ribosomal subunit → inhibits protein synthesis (extracellular bacilli only)

Pharmacokinetics (ADME)

Drug	Absorption	Distribution	Metabolism	Excretion
Isoniazid	Well absorbed orally	Enters CNS and tissues	Hepatic (acetylation)	Renal (adjust in renal failure)
Rifampicin	Good oral bioavailability	Wide, CSF penetration	Hepatic (induces CYP450)	Bile/urine
Pyrazinamide	Well absorbed	Good CSF penetration	Hepatic	Renal (adjust in renal failure)
Ethambutol	Good oral absorption	Enters most tissues, not CNS well	Minimal	Renal (adjust dose)
Streptomycin	Not absorbed orally (IM/IV only)	Extracellular fluid only	Not metabolized	Renal (unchanged)

Note: Dose adjustment is required in renal dysfunction for most except rifampicin.

Pharmacodynamics

- **Isoniazid, rifampicin, pyrazinamide**: Bactericidal
- **Ethambutol**: Bacteriostatic
- **Streptomycin**: Bactericidal (especially extracellular organisms)
- Combination therapy enhances bactericidal effect and prevents resistance

Therapeutic Uses

Standard Regimen for Drug-Sensitive Pulmonary TB (DOTS):

- **2HRZE / 4HR**
  - **Intensive phase (2 months)**: Isoniazid + Rifampicin + Pyrazinamide + Ethambutol
  - **Continuation phase (4 months)**: Isoniazid + Rifampicin

Other Uses:

- **Extrapulmonary TB**: Same regimen but may require longer duration (e.g., TB meningitis: 9–12 months)
- **Latent TB infection (LTBI)**: Isoniazid alone (6–9 months) or Rifampicin (4 months)

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- **Multidrug-resistant TB (MDR-TB)**: Requires 5–7 drugs including second-line agents (18–24 months)
- **TB in HIV**: Same drugs, adjusted for interactions with antiretrovirals

Adverse Effects

Isoniazid (INH):

- Hepatotoxicity
- Peripheral neuropathy (prevented by pyridoxine supplementation)
- Rash, fever, lupus-like syndrome
- Hemolysis in G6PD deficiency

Rifampicin:

- Hepatotoxicity
- Orange discoloration of urine, sweat, tears
- Potent enzyme inducer → drug interactions
- Flu-like syndrome (intermittent dosing)

Pyrazinamide:

- Hepatotoxicity
- Hyperuricemia → gout
- Arthralgia, photosensitivity

Ethambutol:

- **Optic neuritis** → ↓ visual acuity, red-green color blindness (reversible)
- Rash, joint pain

Streptomycin:

- Ototoxicity (vestibular and cochlear)
- Nephrotoxicity
- Neuromuscular blockade (rare)

Contraindications

Drug	Contraindications
Isoniazid	Severe liver disease; hypersensitivity
Rifampicin	Liver failure; concurrent use with protease inhibitors (adjust ART)
Pyrazinamide	Severe liver disease; gout
Ethambutol	Optic neuritis; children too young to assess vision

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Streptomycin	Pregnancy; renal impairment; hearing loss

Drug Interactions

Rifampicin:

- **Potent inducer of CYP450**
  - ↓ efficacy of oral contraceptives, warfarin, antiretrovirals
- Avoid concurrent use with protease inhibitors (unless adjusted)

Isoniazid:

- Inhibits metabolism of phenytoin → toxicity
- Additive hepatotoxicity with rifampicin, alcohol

Others:

- Ethambutol and streptomycin have minimal drug interactions

Dose and Route of Administration

- (**Adult doses** unless otherwise specified)

Drug	Dose	Route
Isoniazid	5 mg/kg/day (max 300 mg)	Oral
Rifampicin	10 mg/kg/day (max 600 mg)	Oral
Pyrazinamide	15–30 mg/kg/day (max 2 g)	Oral
Ethambutol	15–25 mg/kg/day	Oral
Streptomycin	15 mg/kg/day	IM/IV

- **Note:** Fixed-dose combinations (FDCs) are available to improve compliance.
- Adjust dose based on weight and renal function, especially for ethambutol and streptomycin.

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