Drug Treatment of Tuberculosis

Dr Munir Gharaibeh, MD, PhD, MHPE
Department of Pharmacology
School of Medicine
December 2021

Drug Treatment of Tuberculosis

Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV/AIDS). In 2018, 1.7 billion people were infected by TB bacteria.

Recommended Duration of Therapy

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥24

Antituberculous Agents

Primary or First Line Drugs:

Isoniazid (INH)

Rifampin "Rifadin" or "Rimactane"

Ethambutal

Pyrazinamide

Streptomycin: in patients that have previously been treated for TB.

Isoniazid(INH)

- Most active.
- Small molecule, water soluble,
- Structurally related to Pyridoxine.
- Prodrug, activated by KatG(the mycobacterial catalase-peroxidase).
- Blocks mycolic acid synthesis, and consequently mycobacterial cell wall synthesis, leading to a bactericidal effect in growing TB cells.

Isoniazid (INH)

- When used alone, resistance is 1 in 10^6.
- A TB lesion usually contains more than 10^8 cells.
- When used in combination, the probability of resistance will be 1 in

$$10^6 * 10^6 = 10^{12}.$$

- Readily absorbed
- Widely distributed, penetrates into macrophages.
- Metabolized by acetylation:
  - Slow and Fast Acetylators

Isoniazid(INH)

- **Adverse Reactions:**

Hepatitis: in about 1%

Anorexia, N,V, jaundice, pain, death.

Depends on age, alcohol use, and pregnancy

Neuropathy:10-20%

More in slow acetylators, malnutrition, alcoholism, DM, AIDS, uremia.

Due to pyridoxine deficiency.

Neurotoxicity: Memory loss, Psychosis, Seizures.

Hematologic, Tinnitus, GIT, Interactions

Rifampin

- ***Stretomyces miditerranei.***
- **Gram+ve and –ve**
- **Mycobacteria, enterococci and chlamydia.**
- **Binds to the beta subunit of bacterial DNA-dependant RNA polymerase and therefore inhibits RNA synthesis.**

Rifampin

- Bactericidal
- Well absorbed, highly bound to proteins.
- Widely distributed.
- Hepatic metabolism and exhibits enterohepatic recirculation.

Uses of Rifampin

- TB
- Leprosy
- Meningococcal Carrier State
- Prophylaxis in *H.influenzae.*
- Serious Staph osteomyelitis and valve endocarditis.
- Was *loosely used in the treatment of Staph infections.*

Toxicity of Rifampin

- Imparts harmless orange color to secretions(tears, urine, sweat).
- Nephritis
- Rashes
- Hepatitis
- Flu-like syndrome
- Liver Enzyme Inducer, so can lower serum levels of many drugs

Streptomycin

- First aminoglycoside antibiotic, 1943.
- Primary---Second-line------ Primary anti-tuberculus agent.
- Plague, Tuleremia, Brucellosis.
- Endocarditis.

Toxic:

Allergy: Fever, Rashes

Pain, after i.m. injection.

Vestibular toxicity---- Irreversible.

Antituberculous Agents

Secondary or Second Line Drugs:

- Ethionamide
- Capreomycin
- Cycloserine
- Para-Amino-Salicylic Acid (PAS)
- Amikacin
- Flouroquinolones
- Linezolid
- Rifabutin
- Rifapentine

Indications for Secondary or Second Line Drugs

- 1. Resistance to first –line drugs.
- 2. Failure of clinical response to conventional therapy.
- 3. Occurrence of serious treatment-limiting adverse drug reactions.
- 4. When expert guidance is available to deal with the toxic effects to second line drugs.

Secondary or Second Line Drugs

Ethionamide:

Related to Isoniazid

Blocks mycolic acid synthesis

Oral, Good distribution

Poorly tolerated:

- Severe GIT irritation
- Neurotoxic
- Hepatotoxic

Secondary or Second Line Drugs

Capreomycin:

Peptide protein synthesis inhibitor

Injectable

Nephrotoxic, ototoxic

Local pain and sterile abscesses may occur.

Secondary or Second Line Drugs

Cycloserine:

Inhibits cell wall synthesis.

Peripheral neuropathy and CNS toxicity including depression and psychotic reactions.

Secondary or Second Line Drugs

Para-Amino-Salicylic Acid (PAS):

Folate synthesis antagonist

Well absorbed

Dose 8-12 gm/day, *Too large !!!*

Widely distributed, except CNS

Excreted in urine.

GI toxicity

Hypersensitivity reactions

Crystalluria

Secondary or Second Line Drugs

- **Amikacin:**

Another aminoglycoside antibiotic.

Multidrug-resistant strains

Atypical mycobacteria

Secondary or Second Line Drugs

- **Flouroquinolones:**

Are an important addition

Resistance develops rapidly if used alone.

Secondary or Second Line Drugs

Linezolid:

Multidrug-resistant strains.
Bone marrow suppression
Irreversible peripheral and optic neuropathy.
Drug of last resort

Secondary or Second Line Drugs

Rifabutin
Rifapentine

Related to Rifampin.

Inhibit bacterial RNA polymerase.

Both, like Rifampin, are inducers for CYP P450 enzymes. But Rifabutin is less potent inducer.

Rifabutin is indicated in place of Rifampin in the treatment of TB in HIV-infected patients receiving protease inhibitor or nonnucleoside reverse transcriptase inhibitor (e.g. efavirenz)

Drug-Resistant TB (3)

Mono-resistant	Resistant to any one TB treatment drug
Poly-resistant	Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)
Multidrug resistant (MDR TB)	Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
Extensively drug resistant (XDR TB)	Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)

- Annually, 9 million cases are recorded.
- 5% of these are multi drug-resistant tuberculosis.
- Forty-nine percent of those with XDR-TB died compared to 19 percent of patients with ordinary MDR-TB,


IT CAN TAKE
DAY 1
20 pills swallowed + 1 painful injection
START
DAY 240
4,800 pills swallowed
240 painful injections received
DAY 365
7,300 pills swallowed
DAY 730
14,600 pills swallowed
FINISH
2 YEARS
TO TREAT DRUG-RESISTANT TB
WE NEED BETTER TREATMENT NOW