Anti TB Drugs

First Line drugs (primary)

Second Line drugs (secondry)

Indication :
1- Resistance to First Line drugs
2- Failure of clinical response to conventional therapy
3- occurrence of Serious treatment-limiting adverse drug reactions
4- Availability of expert guidance to manage toxic effect.

There are about 9 million new cases annually.
TB killed 1.7 million people worldwide in 2006.

Isoniazid (INH)

most active

MOA:
*Prodrug, activated by KatG (mycobacterial catalase-peroxidase).
• Blocks mycolic acid synthesis,disrupting mycobacterial cell wall synthesis and leading to a bactericidal effect in actively growing Mycobacterium tuberculosis cells.

Adverse Effect :
1- Hepatitis (1%): anorexia,nausea, vomiting, jaundice, pain, and in severe Cases lead to death //Depend on with age, alcohol use, and pregnancy.
2- Neuropathy (10–20%): More in slow acetylators ,and in patients have malnutrition, alcoholism, DM, AIDS, or uremia // cause: due to pyridoxine deficiency.
3-Neurotoxicity: memory loss, psychosis,and seizures.
• Other: Hematologic ,tinnitus, GIT , and drug interactions.

Notes:
• Small molecule, water-soluble, and structurally related to pyridoxine.
• TB lesions typically contain more than 10^8 bacilli.
• Resistance likelihood:
• Monotherapy: 1 in 10^6
• Combination therapy: Reduces resistance to 1 in 10^{12}
• Readily absorbed and widely distributed, including penetration into macrophages.
• Metabolized by acetylation: Slow and fast acetylators.

Rifampin / Rifadin /Rimactane

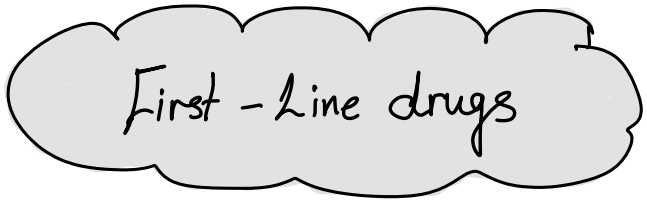
Derived from Streptomyces mediterranei.
MOA: 1- Binds to the beta subunit of bacterial RNA polymerase and inhibiting RNA synthesis.
2-Bactericidal.

Indications:
• Tuberculosis (TB).
• Leprosy.
• Meningococcal carrier state.
• Prophylaxis for Haemophilus influenzae.
• Serious staphylococcal infections, including osteomyelitis and valve endocarditis.

Toxicity:
1-Imparts harmless orange color to secretions (tears, urine, sweat).
2-Rashes.
3-Hepatitis.
4-Flu-like syndrome.

5-Liver enzyme inducer: Can lower serum levels of many drugs.

Notes:
• Active against Gram (+), Gram (-) bacteria, mycobacteria, enterococci, and chlamydia.
• Well absorbed, highly protein-bound, and widely distributed.
• Hepatic metabolism and exhibits enterohepatic recirculation.



Ethambutol

Streptomycin

Primary - second line - primary anti TB agent

Uses:
1-Tuberculosis.
2-Plague.
3-Tularemias حمى الأرانب (an infectious disease caused by Francisella tularensis) (symptoms:fever, skin , large lymph nodes).
4-Brucellosis (malta fever).
5-Endocarditis.

Adverse Effect:
1- Allergy: Fever, rashes, and pain following intramuscular injection.
2- Vestibular toxicity: Irreversible.
3-Nephrotoxicity.

Pyrazinamide

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

Ethionamide

* Related to Isoniazid
- oral
- Good distribution.

MOA : Blocks mycolic acid synthesis

Adverse effect : Poorly tolerated:
1- Severe gastrointestinal (GIT) irritation.
2- Neurotoxicity.
3- Hepatotoxicity.

Capreomycin

Injectable

MOA: Peptide protein synthesis inhibitor

Adverse effect:
1- Nephrotoxicity.
2- Ototoxicity.
3- Local pain and sterile abscesses may occur.

Cycloserine

MOA : Inhibits cell wall synthesis

Adverse Effect:

1- Peripheral neuropathy.
2-CNS toxicity, including depression and psychotic reactions

Para-Amino-Salicylic Acid (PAS)

- Well absorbed.
- Dose: 8-12 gm/day.
- Widely distributed, except in the CNS.
- Excreted in urine.

MOA: Folate synthesis antagonist

Adverse effect:
1-GI toxicity.
2-Hypersensitivity reactions.
3-Crystalluria.

Second - line drugs

Amikacin

- **Active against :** 1-multidrug-resistant strains.
2-atypical mycobacteria.

Fluoroquinolones

* An important addition to TB treatment
* Resistance develops rapidly if used alone

Linezolid

Drug for last resort (الحل الأخير)
Effective against multidrug-resistant strains

AE:

1-Bone marrow suppression.
2- Irreversible peripheral and optic neuropathy.

Rifabutin & Rifapentine

- Related to Rifampin.
- Both Rifabutin and Rifapentine are inducers of CYP P450 enzymes, though Rifabutin is a less potent inducer.
- Rifabutin is used in place of Rifampin for the treatment of tuberculosis (TB) in HIV-infected patients receiving protease inhibitors or non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz).
- Inhibit bacterial RNA polymerase

Atypical Mycobacteria (Nontuberculus Mycobacteria)

- Account for 10% of clinicalisolates.
- Exhibit distinctive laboratory characteristics.
- Found in the environment.
- Not transmissible from person to person.
- Less susceptible to drugs.

M. tuberculosis complex

* Drugs :
  1- Erythromycin
  2- Sulphonamides
  3- Tetracycline

M. avium Complex (MAC)

* important and common cause disseminated TB in late stages of AIDs.
* Drugs : Azithromycin / clarithromycin + Ethambutol + ciprofloxacin

- 5% of these cases are drug-resistant tuberculosis.
- Mortality rates:
- 49% for extensively drug-resistant TB (XDR-TB).
- 19% for multidrug-resistant TB (MDR-TB).

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)