Antituberculous Agents

Primary or First Line Drugs:
Isoniazid (INH)
Rifampin “Rifadin” or “Rimactane”
Ethambutal
Streptomycin
Pyrazinamide
Isoniazid (INH)

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

- TB lesion contains more than $10^8$ bacilli
- If one drug is used, resistance is 1 in $10^6$
- When used in combination, the probability of resistance is $10^6 \times 10^6 = 10^{12}$.
- Readily absorbed
- Widely distributed.
- Acetylated: Slow and Fast Acetylators
Isoniazid (INH)

- **Adverse Reactions:**
  - *Hepatitis:* in about 1%
    - Anorexia, N,V, jaundice, pain, death.
    - Depends on age, alcohol, pregnancy
  - *Neuropathy:* 10-20%
    - More in slow acetylators, malnutrition, alcoholism, DM, AIDS, uremia.
    - Due to increased pyridoxine excretion.
  - **Neurotoxicity:** Memory loss, Psychosis, Seizures.
  - **Hematologic, Tinnitus, GIT, Interactions**
Rifampin

- *Streptomyces 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.
Rifampin

- Orange color
- Nephritis
- Rashes
- Hepatitis
- Light chain proteinurea
- Flu-like syndrome
- Liver Enzyme Inducer, so can lower serum levels of many drugs
Streptomycin

- Primary---Second-line------ Primary anti-tuberculosis agent.
- Plague, Tuleremia, Brucellosis.
- Endocarditis.

Toxic:
Allergy: Fever, Rashes
Pain, after i.m injection.
Vestibular toxicity---- Irreversible.
Nephrotoxicity
Antituberculous Agents

Secondary or Second Line Drugs:

- Ethionamide
- Capreomycin
- Cycloserine
- Para-Amino-Salicylic Acid (PAS)
- Amikacin
- Fluoroquinolones
- 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.
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.
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
- Widely distributed, except CNS
- Excreted in urine.
- GI toxicity
- Hypersensitivity reactions
- Crystalluria
Secondary or Second Line Drugs

- **Amikacin:**
  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
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)
Atypical Mycobacteria (Nontuberculosis Mycobacteria)

- 10% of clinical isolates.
- Distinctive laboratory characteristics.
- Present in the environment.
- Not communicable from person to person.
- Less susceptible to drugs.
Atypical Mycobacteria (Nontuberculous Mycobacteria)

- **M.tuberculosis complex:**
  - Erythromycin
  - Sulphonamides
  - Tetracycline

- **M.avium complex:**
  - Important and common cause of disseminated TB in late stages of AIDS.
  - Azithromycin or Clarithromycin, plus
  - Ethambutal, plus
  - Ciprofloxacin