1st Line Drugs		
Drug	**Notes**	**Adverse Effects**
Isoniazid (INH)	- **Most active**, readily absorbed, widely distributed, and penetrates into macrophages (where TB resides); thus, it is not needed IV. - A small molecule, water-soluble, structurally related to **Pyridoxine**. - Metabolized by hepatic acetylation: Slow and Fast Acetylators. - A **Prodrug**, activated by **KatG** (the mycobacterial catalase-peroxidase). - KatG is a heme enzyme considered important for virulence, which is also responsible for the activation of the anti-tuberculosis pro-drug isoniazid. - **Blocks mycolic acid synthesis**, and consequently the mycobacterial cell wall synthesis, leading to a **bactericidal** effect in growing TB cells. - When used alone, resistance is 1 in 10^6. - When used in combination, the probability of resistance will be 1 in 10^{12}. - A TB lesion usually contains more than 10^8 cells.	- **Hepatitis**: in about 1%: More in **fast** acetylators. Anorexia, nausea, vomiting, jaundice, pain, and death. Depends on age, alcohol use, and pregnancy - **Neuropathy**: 10-20% Due to pyridoxine deficiency. More in **slow** acetylators, malnutrition, alcoholism, DM, AIDS, and uremia. - **Neurotoxicity**: Memory loss, Psychosis, Seizures. - Hematologic, Tinnitus, GIT, drug-drug interactions. - In Isoniazid toxicity, we use Pyridoxine.
Rifampin	- Rifamycins are antibiotics derived from Streptomyces mediterranei. - Has a wide action: acts on both Gram +ve and –ve // Mycobacteria // enterococci // chlamydia. - Binds to the beta subunit of bacterial DNA-dependent RNA polymerase **inhibiting RNA synthesis.** - **Bactericidal**, well-absorbed, widely distributed, and highly bound to proteins. - Undergoes hepatic metabolism and exhibits enterohepatic recirculation. - **Used for:** **a-** TB, Leprosy, and Meningococcal Carrier State. **b-** Prophylaxis in H. influenzae. **c-** Serious Staph osteomyelitis, and valve endocarditis. **d-** Loosely used in the treatment of Staph infections.	- 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 (drug-drug interactions).

Streptomycin	- **First** aminoglycoside antibiotic, 1947. - Primary, then it became Second-line due to toxicity. Nowadays it is considered a Primary anti-TB agent. - **Used for:** Gram -ve, Endocarditis, Plague, Tularemia, and Brucellosis. ⇨ Tularemia: is a severe infectious bacterial disease of animals transmissible to humans, characterized by ulcers at the site of infection, fever, and loss of weight.	- Allergy: Fever, Rashes. - Pain after IM injection; requires supervision. - Vestibular toxicity (Irreversible). - Nephrotoxicity.

⇨ 1st line drugs include: Isoniazid (INH), Rifampin (Rifadin or Rimactane), Ethambutol, Streptomycin, and Pyrazinamide.

2nd Line Drugs

Indications for Second Line Drugs:

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

Drug	Notes	Adverse Effects
Ethionamide	- **Related to Isoniazid**. - Blocks mycolic acid synthesis. - Oral, with good distribution.	- Poorly tolerated: **a-** Severe GIT irritation **b-** Neurotoxic **c-** Hepatotoxic
Capreomycin	- Peptide protein synthesis inhibitor. - Injectable.	- Nephrotoxic and ototoxic. - Local pain and sterile abscesses may occur.
Cycloserine	- Inhibits cell wall synthesis.	- Peripheral neuropathy and CNS toxicity including depression and psychotic reactions.
Para-Amino-Salicylic Acid (PAS)	- It is a weak drug. - Folate synthesis antagonist, well absorbed. - Dose 8-12 gm/day, **TOO LARGE**. - Widely distributed, **except** to the CNS. - Excreted in the urine.	- GI toxicity. - Hypersensitivity reactions. - Crystalluria, predisposing to kidney stones.
Amikacin	- Another aminoglycoside antibiotic. - **Used for:** Multidrug-resistant strains and Atypical mycobacteria.	

Fluoroquinolones	- Important add-ons. - Resistance develops rapidly if used alone.	
Linezolid	- For multidrug-resistant strains. - Drug of **last** resort.	- Bone marrow suppression - Irreversible peripheral and optic neuropathy.
Rifabutin **Rifapentine**	- Related to Rifampin. - They **inhibit bacterial RNA polymerase**. - Both, like Rifampin, are inducers for CYP P450 enzymes. But Rifabutin is a 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
(Non-tuberculous Mycobacteria)

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

M. tuberculosis complex	M. avium complex
- **Drugs**: **a-** Erythromycin **b-** Sulphonamides **c-** Tetracycline	- An important and common cause of disseminated TB in the late stages of AIDS. - **Drugs:** Azithromycin or Clarithromycin + Ethambutol + Ciprofloxacin.

- TB used to be a disease of the low-socioeconomic countries, but it appears now in high-socioeconomic countries as well.
- Drugs are taken in combination for a long period. Single therapy is not efficient and would result in resistance immediately.

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

- Annually, 9 million TB cases are recorded. 5% of these are multidrug-resistant tuberculosis.
- 49% percent of those with extensively drug-resistant TB (XDR-TB) died compared to 19 % of patients with multidrug-resistant tuberculosis (MDR-TB).
- TB killed 1.7m people worldwide in 2006.

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)

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