Drug Treatment of Tuberculosis

Drug	MOA	Uses	Side Effects	Notes
First Line Drugs (Primary)				
Isoniazid (INH)	- A **prodrug** activated by a mycobacterial catalase–peroxidase (KatG) -The activated Isoniazid **blocks mycolic acid synthesis**, and consequently mycobacterial cell wall synthesis, leading to a **bactericidal** effect	-Treatment of TB	-**Hepatitis**: in about 1% (in fast acetylators) -Anorexia, nausea, vomiting, jaundice, pain, and death (depend on age, alcohol use, pregnancy) -**Neuropathy**: 10-20% (due to **pyridoxine (Vit B6) deficiency**): occurs more in slow acetylators, malnutrition, alcoholism, DM, AIDS, and uremia -**Neurotoxicity**: memory loss, psychosis, and seizures -Hematologic, tinnitus, GIT, and drug interactions	- Most active, it is a small molecule and water soluble - Structurally related to Pyridoxine (Vit B6) - Readily absorbed and widely distributed so it penetrates into macrophage easily -Metabolized by acetylation: there are slow and fast acetylators
Rifampin	-Binds to the beta subunit of bacterial **RNA polymerase** and therefore inhibits RNA synthesis → prevent the synthesis of bacterial proteins -**Bactericidal** (dose defendant)	-TB -Leprosy -Meningococcal Carrier State -**Prophylaxis** in H.influenzae -Serious Staph Osteomyelitis -**Drug of choice** for valve endocarditis -Streptomyces mediterranei -Enterococci and chlamydia	✸**Toxicity**: - **Mild**: Imparts harmless orange color to secretions (tears, urine, sweat), rashes and flu-like syndrome -**Serious**: Can cause hepatitis and is a liver enzyme inducer (stimulates liver enzyme activity → decrease in the serum levels of many drugs)	- Well absorbed, highly bound to proteins, and widely distributed -Metabolized in the liver and exhibits enterohepatic recirculation -If only a small dose is given or the period of treatment is short, the effect becomes bacteriostatic -In Jordan, use restricted for TB
Streptomycin	-Binds irreversibly to **small subunit of rRNA**	-Used for plague, Tularemia, Brucellosis, and endocarditis	✸**Toxicity:** -Allergy, fever, rashes, and pain after IM injection -**Vestibular toxicity (Irreversible)** -Nephrotoxicity	-A second-line anti-tuberculous agent but it could be used as a first line agent
Second Line Drugs				
Ethionamide	-Related to Isoniazid: it blocks mycolic acid synthesis		-**Poorly tolerated**: severe GIT irritation, neurotoxic and hepatotoxic	-Given orally and has a good distribution
Capreomycin	-Peptide protein synthesis inhibitor		Nephrotoxic, ototoxic, local pain (at injection site) and sterile abscesses	-Injectable
Cycloserine	-Inhibits cell wall synthesis (bactericidal)		-Peripheral **neuropathy and CNS toxicity:** depression and psychosis	-We give it to the patient in the hospital to ensure supervision
Amikacin		-Used with **Atypical mycobacteria and multidrug-resistant strains**		

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Para-Amino-Salicylic Acid (PAS)	-Folate synthesis antagonist		-GI toxicity, hypersensitivity reactions, and crystalluria	-Well absorbed, dose 8-12 gm/day -Widely distributed, except in CNS -Excreted in Urine
Fluoroquinolone		-Important addition to the treatment regimen		**Resistance develops rapidly if used alone
Linezolid		- Used for multidrug-resistant strains - **Drug of last resort**	-Bone marrow suppression, irreversible peripheral and optic neuropathy	
Rifabutin & Rifapentine	-Related to Rifampin: inhibit bacterial RNA polymerase	-Rifabutin is indicated in place of Rifampin in the **treatment of TB in HIV-infected patients** receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors (E.G **efavirenz** which are metabolized by CYP450)	-Like rifampin: inducers for CYP P450 enzymes (Rifabutin is a less potent inducer)	

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