Pharma Lect 2:

Isoniazid:

- Most active
- First line
- Small molecule, water soluble
- Structurally related to pyridoxine
- Prodrug activated by KatG (mycobacterial catalase peroxidase)
- Blocks mycolic acid synthesis and consequently mycobacterial cell wall synthesis, leading to a bactericidal effect in growing TB cells
- When used alone, resistance is 1 in 10^6
- Readily absorbed
- Widely distributed, penetrates in macrophages
- Metabolized by acetylation: slow and fast acetylators
- **Adverse effects:**
    - Hepatitis in 1%: Depends on age, alcohol, and pregnancy
        - Anorexia
        - Jaundice,
        - pain, death
    - Neuropathy 10-20%:
        - More common in slow acetylators, Malnutrition, Alcoholism, DM, aids, Uremia
    - Neurotoxicity:
        - Memory loss
        - Psychosis
        - Seizures
    - Hematologic:
        - Tinnitus
        - GIT interaction

Rifampin:

- Streptomyces mediterranei
- First line
- Gram + and -
- Mycobacteria, enterococci, chlamydia
- Binds to the beta subunit of bacterial DNA-dependent RNA polymerase and therefore inhibits RNA synthesis
- Bactericidal
- Well absorbed, highly bound to proteins
- Widely distributed
- Hepatic metabolism and exhibits enterohepatic recirculation
- **Uses:**
    - Leprosy
    - Meningococcal carrier state

    - Prophylaxis in H influenza
    - Serious staph osteomyelitis and value endocarditis
    - Was loosely used in the treatment of staph infection
- **Adverse Effects:**
    - Nephritis
    - Rashes
    - Hepatitis
    - Flu-like syndrome
    - Liver enzyme inducer, so can lower serum levels of many drugs
    - Imparts harmless orange color to secretions:
        - Tears
        - Urine
        - Sweat

Streptomycin:

- First aminoglycoside antibiotic, 1943
- Primary–second line—primary anti-tuberculosis agent
- In patients who have previously been treated for TB
- Endocarditis
- **Adverse Effects:**
    - Allergy:
        - Fever
        - Rashes
    - Pain after Intramuscular injection
    - Vestibular toxicity→ irreversible

Lecture 3:

Overview of second line drugs:

Ethionamide
Capreomycin
Cycloserine
Para-amino-sialicylic acid (PAS)
Amikacin
Fluoroquinolones
Linezolid
Rifabutin
Rifapentine

When to take **second** line drugs:

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

Ethionamide:

- Related to isoniazid
- Blocks mycolic acid synthesis
- Oral, good distribution
- **Adverse effects:**
    - Severe GIT irritation
    - Neurotoxic
    - hepatotoxic

Capreomycin:

- Peptide protein synthesis inhibitor
- Injectable
- **Adverse effects:**
    - Nephrotoxic
    - Ototoxic
    - Local pain and sterile abscesses may occur

Cycloserine:

- Inhibits cell wall synthesis
- **Adverse Effects:**
    - Peripheral neuropathy
    - CNS toxicity
    - Depression
    - Psychotic reactions

Para-amino-salicylic Acid (PAS):

- Folate synthesis antagonist
- Well absorbed
- Dose 8-12 gm/day TOO LARGE!!
- Widely distributed, EXCEPT CNS
- Excreted by urine
- **Adverse Effects:**
    - GI toxicity
    - Hypersensitivity reactions
    - Crystalluria

Amikacin:

- Aminoglycoside antibiotic
- Multidrug resistant strain
- Atypical by bacteria

Fluoroquinolones:

- Important addition
- Resistance develops rapidly if used alone

Linezolid:

- Drug of LAST resort
- **Adverse Effects:**
    - Multidrug resistant strains
    - Bone marrow suppression
    - Irreversible peripheral and optic neuropathy

Rifabutin/ Rifapentine:

- Related to rifampin
- Inhibits bacterial RNA polymerase
- Inducers of CYP P450
- Rifabutin is LESS potent inducer and indicated in place of rifampin in treatment of TB in HIV infected patients receiving protease inhibitor or nonnucleoside reverse transcriptase inhibitor (efavirenz)