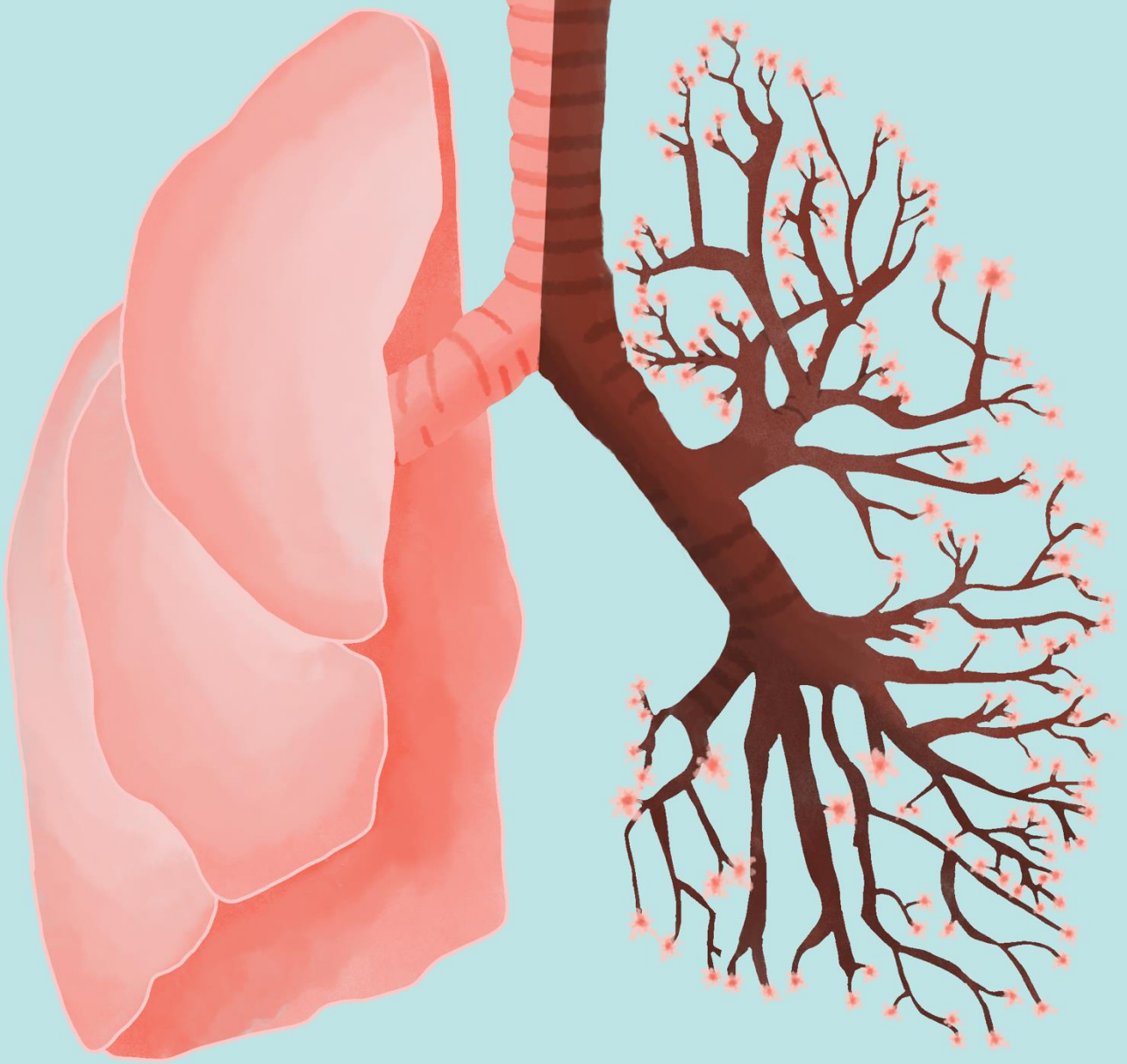
RESPIRATORY SYSTEM PHARMACOLOGY



Title: Sheet 3&4 – Drug Treatment of Tuberculosis

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Drug Treatment of Tuberculosis

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

Recommended Duration of Therapy

- The length of treatment for tuberculosis ranges from 6 months to 2 years.
- We use more than one antibiotic to:
  - ✓ Decrease the resistance of the bacteria.
  - ✓ Decrease the dose for each antibiotic which will decrease the side effects for each antibiotic.

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

Primary or First Line Drugs

- We use at least two of them in the first line of treatment and we may change the drugs or their doses according to the response of the patient.
- -Isoniazid (INH) -Rifampin "Rifadin" or "Rimactane" -Ethambutol
- -Streptomycin -Pyrazinamide

Isoniazid (INH)

- Most active, it is a small molecule and water soluble (so it's widely distributed and very efficient).
- Structurally related to Pyridoxine (Vit B6).
- **MOA**: 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 in growing TB cells.

- TB lesion contains more than 10^8 bacilli (cells).
- When it used alone, the probability of resistance is 1 in 10^6.
  When it used in combination, the resistance will be 1 in $10^6 * 10^6 = 10^{12}$.

- Readily absorbed and widely distributed so it penetrates into macrophage easily.
- Metabolized by acetylation: **Slow and Fast Acetylators**
  Metabolism is needed to convert it from the inactive (prodrug) to the active form and for the clearance of the drug.

- **Adverse Reactions**
  - ✓ **Hepatitis**: in about 1%**.**
  - ✓ Anorexia, nausea, vomiting, jaundice, pain, and death. These depend on age, alcohol use, and 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.

Rifampin

- Efficient for treatment of Streptomyces mediterranei, Gram +ve and –ve bacteria, Mycobacteria, enterococci and chlamydia (in Jordan it's restricted for TB).
- Binds to the **beta subunit** of **bacterial RNA polymerase** and therefore **inhibits RNA synthesis** (including mRNA) and this will prevent the synthesis of bacterial proteins.
- **Bactericidal** (Related to the dose and the frequency of intake of the drug. If only a small dose is given or in a short treatment period, the drug will be bacteriostatic.)
- Well absorbed, highly bound to proteins, and widely distributed.
- Metabolized in the liver and exhibits enterohepatic recirculation. (we should be mindful of this when calculating dosage)

- **Uses of Rifampin**
  - ✓ **TB**
  - ✓ **Leprosy**
  - ✓ **Meningococcal Carrier State**
  - ✓ **Prophylaxis in H.influenzae**.
  - ✓ **Serious Staph Osteomyelitis**: Osteomyelitis (OM) is an infection of bone. Symptoms may include pain in a specific bone with overlying redness, fever, and weakness. The long bones of the arms and legs are most commonly involved in children while the feet, spine, and hips are most commonly involved in adults
  - ✓ **Valve endocarditis (drug of choice)**: It is an inflammation of the inner tissues of the heart (the endocardium) and usually of the valves. It is caused by infectious agents, or pathogens, which are largely bacterial.

- **Toxicity of Rifampin**
  - ✓ 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**. This means it will stimulate liver enzyme activity, which will lead to a decrease in the serum levels of many drugs.

Streptomycin

- A second-line anti-tuberculous agent but it could be used as a first line agent.
- Used for plague, Tularemia حمى الارانب, Brucellosis, and endocarditis.
- **Toxicity**
  - ✓ Allergy, fever, rashes, and pain after IM injection.
  - ✓ **Vestibular toxicity (Irreversible).**
  - ✓ Nephrotoxicity
- Tularemia is an infectious disease caused by the bacterium Francisella tularensis. Symptoms may include fever, skin ulcers, and large lymph nodes.

Secondary or Second Line Drugs: (be familiar with them)

- -Ethionamide -Capreomycin -Cycloserine -Amikacin
- -Fluoroquinolones -Linezolid -Rifabutin -Rifapentine
- -Para-Amino-Salicylic Acid (PAS)

Indications for Secondary or Second Line Drugs (used when there is:)

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.

Ethionamide

- Related to Isoniazid in the mechanism as it **blocks mycolic acid synthesis**
- Given orally and has a good distribution.
- Poorly tolerated: severe GIT irritation, neurotoxic and hepatotoxic.

Capreomycin

- **Peptide protein synthesis inhibitor**
- Injectable (can cause an issue with compliance)
- Side effects: nephrotoxic, ototoxic, local pain (at injection site) and sterile abscesses may occur.

Cycloserine

- **Inhibits cell wall synthesis (bactericidal).**
- Peripheral neuropathy and CNS toxicity including depression and psychotic reactions.
- We give it to the patient in the hospital to ensure medical supervision.

Para-Amino-Salicylic Acid (PAS)

- **Folate synthesis antagonist**
- Well absorbed, dose 8-12 gm/day
- Widely distributed, except in the CNS.
- Excreted in urine (need to be mindful of the dose if there are kidney problems).
- Side effects: GI toxicity, hypersensitivity reactions, and crystalluria

Amikacin

- Used **with Atypical mycobacteria** and multidrug-resistant strains.

Fluoroquinolones

- Are an important addition to the treatment regimen.
- **Resistance develops rapidly if used alone**.

Linezolid

- Used for multidrug-resistant strains.
- Side effects: Bone marrow suppression, irreversible peripheral and optic neuropathy.
- **Drug of last resort** الحل الأخير

Rifabutin & Rifapentine

- Related to Rifampin in the mechanism as 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 inhibitors or nonnucleoside reverse transcriptase inhibitors (e.g. efavirenz which are metabolized by CYP P450).

Atypical Mycobacteria (Nontuberculous Mycobacteria)

- Represent 10% of clinical isolates.
- Show distinctive laboratory characteristics.
- Present in the environment and not communicable from person to person.
- Less susceptible to drugs.

1. **M.tuberculosis complex:**
   - ✓ **Erythromycin**, **Sulfonamides** and **Tetracycline**
2. **M.avium complex:**
   - ✓ Important and common cause of disseminated TB in late stages of AIDS.
   - ✓ **Azithromycin** or Clarithromycin, plus **Ethambutol** and **Ciprofloxacin**

- Annually, 9 million cases of TB are recorded.
- 5% of these are drug-resistant tuberculosis. **49% of those with XDR-TB died** compared to 19% of patients with ordinary MDR-TB died.
- The most important thing is to prevent TB, because it is difficult to deal with these drugs for up to two years with their side effects.