Treatment of TB
Objectives

1. Describe the strategies of treatment of T.B.
2. List the major classes of drugs used in treatment of TB.
3. Describe the mechanism of action of these drugs.
4. Describe the pharmacokinetics of these drugs.
5. Describe the pharmacological action of these drugs.
6. List the major adverse effects of these drugs and drug resistance
TB is an infectious disease caused by Mycobacterium Tuberculosis.
# Antituberculosis Drugs

**First-Line Drugs**
- Rifampin
- Isoniazid
- Pyrazinamide
- Ethambutol
- Streptomycin

**New drugs**
- Rifabutin*
- Rifapentine

**Second-Line Drugs**
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin*
- Moxifloxacin*
- Gatifloxacin*
First-line drugs

- **Isoniazid (1952)**
  - Inhibits cell wall synthesis

- **Ethambutol (1961)**
  - Inhibits cell wall synthesis

- **Pyrazinamide (1952)**
  - Exact Target Unclear
  - Disrupts Plasma Membrane
  - Disrupts Energy Metabolism

- **Rifampin (1966)**
  - Inhibits RNA synthesis

**Mycobacterium tuberculosis**

- **Cell Wall Synthesis**
  - Acyl Lipids
  - Mycolic Acid
  - Arabinogalactan
  - Peptidoglycan
  - Plasma Membrane

- **DNA Coiling, Transcription, and Translation**
  - RNA Polymerase
  - DNA Gyrase
  - mRNA
  - DNA
  - Ribosome
  - Protein

- **ATP Synthesis**
  - ATP
**Rifampin**

**Mechanism of Action:**
Rifampin inhibits DNA dependent RNA polymerase of the bacilli. **Bactericidal.**

**Spectrum:** Mycobacteria (TB & Leprosy), Gram +ve & -ve Bacteria, Chlamydia.

**Resistance:**
Due to alteration of the target (DNA dependent RNA polymerase).

**Therapeutic uses:**
1. Treatment of T.B. in combination with Isoniazid.
3. Latent TB
4. Some Resistant Bacterial Infections e.g. Staph.
5- Prophylaxis against H. influenza type B.

**Adverse Effects:**
1. Cholestatic jaundice
3. Orange red color in body excretions.

**Drug interaction:**

Rifampin is an enzyme inducer. Induces hepatic microsomal enzymes: P450 system; accelerates metabolism of many drugs making them less effective or ineffective (↓ Actions of Oral AntiCoagulants, Hypoglycemics, Contraceptives, Digitoxin, Corticosteroids).
**Rifabutin**: For patients receiving medications having unacceptable interactions with rifampin.
**Isoniazid (INH)**
a hydrazide of isonicotonic acid
is bacteriostatic for resting bacilli, bactericidal for growing bacilli.

**Mechanism of action:**
inhibit synthesis of mycolic acids which are part of cell wall structure.

**Clinical uses:** used in prophylaxis (alone), treatment (combined) and latent TB.

**Resistance:**
failure of the drug to penetrate or be taken up by the micro-organism (by active transport system).
Pharmacokinetics:
  enzymatic acetylation in the liver is under genetic control (Fast and slow acetylators).

Adverse Effects: (INH)
1. Idiosyncratic: Systemic lupus erythematosus SLE-like disease.
2. Neurotoxicity: peripheral neuritis which is preventable with pyridoxine !!!
3. Hepatitis.
4. Hypersensitivity.-
**Drug interaction:**
INH is an enzyme inhibitor (decrease metabolism of other drugs).

**Caution:**
People with a deficiency of Glucose-6-phosphate cannot adequately process the drug.
PYRAZINAMIDE:
• Inhibits cell wall synthesis by bacteria

• Bactericidal in acid environment (macrophages).

• It has wide distribution and excellent CSF entry- useful in tuberculosis meningitis

Side effects:  
  a- Hepatotoxic  
  b- Hyperuricemia
ETHAMBUTOI

- Inhibits cell wall synthesis
- Most important function is prevention of resistance, Bacteriostatic.

Clinical uses
- MDT in TB
- TB meningitis

- Side effects: a- Optic Neuritis. b- Hyperuricemia.
**Streptomycin**

is an aminoglycoside antibiotic.

**Mechanism of action:**
- They inhibit protein synthesis by binding to the 30s subunit of the ribosome. Bactericidal.
- The drug accumulated intracellularly in microorganism via O2 dependent uptake, thus anaerobes are resistant.

**Therapeutic uses**
- Uses: Life threatening TB infection, MDR TB
Pharmacokinetics:
Aminoglycosides are polar compounds, not absorbed orally. So given parenterally.

Adverse Effects:
1. Ototoxicity: auditory and vestibular
2. Neurotoxicity.
3. Neuromuscular blocking effect.
# Mechanisms of Action, Resistance, and Adverse Effects

## Table V-1-4. Summary of the Actions, Resistance, and Adverse Effects of the Antitubercular Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanisms of Action and Resistance</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Inhibits mycolic acid synthesis; high level resistance—deletions in katG gene (encodes catalase needed for INH bioactivation); low-level resistance—deletions in inhA gene (encodes acyl carrier protein, the “target”).</td>
<td>Hepatitis (age-dependent), peripheral neuritis (use vitamin $B_6$), hemolysis in G6PD deficiency, SLE in slow acetylators (rare)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Inhibits synthesis of arabinogalactan (cell-wall component)</td>
<td>Dose-dependent retrobulbar neuritis $\rightarrow$ visual acuity and red-green discrimination</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Unknown, but metabolically activated by bacteria—strains lacking the bioactivating enzyme are resistant</td>
<td>Polyarthralgia, myalgia, hepatitis, rash, hyperuricemia, phototoxicity, ↑ porphyrin synthesis</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Protein synthesis inhibition</td>
<td>Deafness, vestibular dysfunction, nephrotoxicity</td>
</tr>
<tr>
<td>DRUG</td>
<td>ADVERSE EFFECTS</td>
<td>COMMENTS</td>
</tr>
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<td>-----------</td>
<td>------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuritis with blurred vision, red-green color blindness</td>
<td>Establish baseline visual acuity and color vision; test monthly.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Hepatic enzyme elevation, hepatitis, peripheral neuropathy</td>
<td>Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with <em>phenytoin</em> and antifungal agents (azols).</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)</td>
<td>Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs</td>
<td>Take baseline hepatic enzyme measurements and CBC count; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Ototoxicity, nephrotoxicity</td>
<td>Do baseline audiography and renal function tests; avoid or reduce doses in patients older than sixty years.</td>
</tr>
</tbody>
</table>

Figure 34.10
Some characteristics of first-line drugs used in treating tuberculosis. CBC = complete blood count.
ALTERNATIVE SECOND LINE DRUGS FOR TUBERCULOSIS

1. In case of resistance to first line agents.
2. In case of failure of clinical response.
3. In case of serious adverse drug reactions
4. when expert guidance is available to deal with the toxic effects.
2nd line treatment
2nd-line drugs

- Isoniazid: Inhibits cell wall synthesis
- Rifampin: Inhibits RNA synthesis
- Thioamides: Inhibit cell wall synthesis
- Cycloserine: Inhibits cell wall synthesis
- PAS: Inhibits synthesis of DNA precursors
- Fluoroquinolones: Inhibit DNA Gyrase
- Cyclic Peptides: Inhibit protein synthesis
- Aminoglycosides: Inhibit protein synthesis

**Mycobacterium tuberculosis**

- Cell Wall Synthesis
  - Acyl Lipids
  - Mycolic Acid
  - Arabinogalactan Peptidoglycan
  - Plasma Membrane

- DNA Coiling, Transcription, and Translation
  - RNA Polymerase
  - DNA Gyrase
  - mRNA
  - Ribosome
  - Protein

- ATP Synthesis
1-para- Aminosalicylic Acid
a structural analog of PABA (p-aminobenzoic acid)

is bacteriostatic inhibits de novo folate synthesis

Adverse Effects:
A-GI irritation (nausea, vomiting)
B-Hypersensitivity reactions Rash Fever
C-hepatotoxicity
D- Nephrotoxic.
E- ↓Thyroid.
2- Capreomycin - - Viomycin – Kanamycin
These are aminoglycosides.

Mechanism of action:
They inhibit protein synthesis by binding to the 30s subunit of the ribosome.

Adverse effects:
A- Nephrotoxic
B- Ototoxic : auditory and vestibular.

Capreomycin has replaced viomycin because of less toxic effects, but all three drugs have the same effects.
3- **Cycloserine:**

**Mechanism of Action:**
block bacterial cell wall synthesis.

**Adverse effects:**
CNS disturbances & neuropathy

4- **ETHIONAMIDE:**
Inhibits cell wall synthesis

**Side effects:**
a- neurotoxicity
b- Hepatotoxic.
Use drug combination:
a- To increase effectiveness.
b- To decrease Toxicity.
c- To decrease resistance.
Directly observed therapy (DOT)

- regimens are recommended in non-compliant patients and in drug-resistant tuberculosis.
Strategy of treatment

1- Rifampicin + Isoniazid + Ethambutol for 2 months
Followed by: Rifampicin + Isoniazid for next 4 months.

OR

2- Rifampicin + Isoniazid + Pyrazinamide for 2 months
Followed by: Rifampicin + Isoniazid for next 4 months.

OR

3- Rifampicin + Isoniazid + Pyrazinamide + Streptomycin or Ethambutol for 2 months
Followed by: Rifampicin + Isoniazid for next 4 months.