Antimycobacterial Drugs

- Mycobacteria are rod-shaped aerobic bacilli
- Multiple slowly, every 18 to 24 hours in vitro.
- Their cell walls contain mycolic acids, which give the genus its name.
- Mycolic acids are very long-chain, β-hydroxylated fatty acids.
- Mycobacteria produce highly lipophilic cell walls that stain poorly with Gram stain.
- Once stained, the bacilli are not decolorized easily by acidified organic solvents. Hence, the organisms are called “acid-fast bacilli.”
- Mycobacterial infections classically result in the formation of slow growing, granulomatous lesions that cause tissue destruction anywhere in the body.
Antimycobacterial Drugs

• **Mycobacterium tuberculosis** can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB).

• In LTBI, the patient is infected with M.tuberculosis but does not have any signs or symptoms of active TB disease.

✓ TB is the leading infectious cause of death worldwide, and over 2 billion people already have been infected.
Anti-mycobacterial Drugs

- TB treatment generally includes **four first-line drugs**
- **Second-line drugs** are typically less effective, more toxic, and less extensively studied.
- They are used for patients who cannot tolerate the first-line drugs or who are infected with resistant TB.

**DRUGS USED TO TREAT TUBERCULOSIS**

- Ethambutol
- Isoniazid
- Pyrazinamide
- Rifabutin
- Rifampin
- Rifapentine

**DRUGS USED TO TREAT TUBERCULOSIS (2nd line)**

- Aminoglycosides
- Aminosalicylic acid
- Bedaquiline
- Capreomycin
- Cycloserine
- Ethionamide
- Fluoroquinolones
- Macrolides
Chemotherapy of Tuberculosis

• M. tuberculosis is slow growing and requires treatment for months to years.

✓ LTBI can be treated for 9 months with isoniazid (INH) monotherapy or with 12 once-weekly doses of INH (900 mg) and rifapentine (900 mg).

✓ In contrast, active TB disease must be treated with several drugs.

✓ Treatment for drug-susceptible TB lasts for at least 6 months

✓ Treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years.
Strategies for addressing drug resistance

- Populations of *M. tuberculosis* contain small numbers of organisms that are naturally resistant to a particular drug.
- Under selective pressure from inadequate treatment, especially from monotherapy, these resistant TB can emerge as the dominant population.
- Multidrug therapy is employed to suppress these resistant organisms.
- The first-line drugs *isoniazid*, *rifampin*, *ethambutol*, and *pyrazinamide* are preferred because of their high efficacy and acceptable incidence of toxicity.
- Active disease always requires treatment with multidrug regimens, and preferably three or more drugs with proven in vitro activity against the isolate.
- Although clinical improvement can occur in the first several weeks of treatment, therapy is continued much longer to eradicate persistent organisms and to prevent relapse.
Strategies for addressing drug resistance

- Standard short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (the intensive phase), followed by isoniazid and rifampin for 4 months (the continuation phase).

- Secondline regimens for MDR-TB (TB resistant to at least isoniazid and rifampin) normally include an aminoglycoside (streptomycin, kanamycin, or amikacin) or capreomycin (all injectable agents),
  - Fluoroquinolone (typically levofloxacin or moxifloxacin).

- Any first-line drugs that remain active, and one or more of the following: cycloserine, ethionamide, or p-aminosalicylic acid.
Figure 41.3
One of several recommended multidrug schedules for the treatment of tuberculosis.
o Patient adherence can be low when multidrug regimens last for 6 months or longer.

o One successful strategy for achieving better treatment completion rates is **directly observed therapy (DOT)**.

o Patients take their medications while being watched by a member of the health care team.

o DOT has been shown to decrease drug resistance and to improve cure rates.

o Most public health departments offer DOT services.
Isoniazid (INH)

- Isoniazid along with rifampin, is one of the two most important TB drugs.

- **Mechanism of Action:**
  - Isoniazid is a prodrug activated by a mycobacterial catalase–peroxidase (KatG).
  - Isoniazid targets the enzymes acyl carrier protein reductase (InhA) and β-ketoacyl-ACP synthase (KasA), which are essential for the synthesis of mycolic acid.
  - Inhibiting mycolic acid leads to a disruption in the bacterial cell wall.

- **Antibacterial Spectrum:**
  - Isoniazid is specific for treatment of M. tuberculosis,
  - The drug is particularly effective against rapidly growing bacilli and is also active against intracellular organisms.
**Resistance**: Resistance follows chromosomal mutations, including

- Mutation or deletion of KatG (producing mutants incapable of prodrug activation),
- Varying mutations of the acyl carrier proteins.
- Over expression of the target enzyme InhA.
  - **Cross resistance** may occur between isoniazid and ethionamide.

**Pharmacokinetics**: Isoniazid is readily absorbed after oral administration.

- Absorption is impaired if isoniazid is taken with food, particularly high-fat meals.
- The drug diffuses into all body fluids.
- Drug concentrations in the cerebrospinal fluid are similar to those in the serum.
- Isoniazid undergoes N-acetylation and hydrolysis, resulting in inactive products.
- Isoniazid acetylation is genetically regulated.
- Excretion is through glomerular filtration and secretion.
Adverse effects:

- **Hepatitis** is the most serious adverse effect associated with isoniazid.

  ✔ If hepatitis goes unrecognized, and if isoniazid is continued, it can be fatal.

- **Peripheral neuropathy** (manifesting as paresthesia of the hands and feet) appears to be due to a relative pyridoxine deficiency. This can be avoided by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B6).

- **Central nervous system** (CNS) adverse effects can occur, including convulsions in patients prone to seizures.

- **Hypersensitivity** reactions with isoniazid include rashes and fever.
Rifamycins: rifampin, rifabutin, and rifapentine

- Rifampin, rifabutin, and rifapentine are all considered rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line oral agents for tuberculosis.

- Rifampin has broader antimicrobial activity than isoniazid and can be used as part of treatment for several different bacterial infections.

- Because resistant strains rapidly emerge during monotherapy, it is never given as a single agent in the treatment of active tuberculosis.

- **Mechanism of action:**
  - Rifampin blocks RNA transcription by interacting with the β subunit of mycobacterial DNA-dependent RNA polymerase.

- **Antimicrobial spectrum:**
  - Rifampin is bactericidal for both intracellular and extracellular mycobacteria.
  - It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis.
- **Resistance**: Resistance to rifampin is caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.

- **Pharmacokinetics**: Absorption is adequate after oral administration.

  - Distribution of rifampin occurs to all body fluids and organs. Concentrations attained in the CSF are variable, often 10% to 20% of blood concentrations.

  - Rifampin can induce hepatic cytochrome P450 enzymes and transporters leading to numerous drug interactions.

  - Elimination rifampin and its metabolites is primarily through the bile and into the feces; a small percentage is cleared in the urine

  - Urine, feces, and other secretions have an orange-red color, so patients should be forewarned.

  - Tears may even stain soft contact lenses orange-red.
Pyrazinamide

- Pyrazinamide is a synthetic, orally effective shortcourse agent used in combination with isoniazid, rifampin, and ethambutol.
- The precise mechanism of action is unclear.
- Pyrazinamide must be enzymatically hydrolyzed by pyrazinamidase to pyrazinoic acid, which is the active form of the drug.
- Some resistant strains lack the pyrazinamidase enzyme.
- The drug distributes throughout the body, penetrating the CSF.
- Pyrazinamide may contribute to liver toxicity.
- Uric acid retention is common but rarely precipitates a gouty attack.
- Most of the clinical benefit from pyrazinamide occurs early in treatment. Therefore, this drug is usually discontinued after 2 months of a 6-month regimen.
Ethambutol

• Ethambutol is **bacteriostatic** and **specific** for mycobacteria.
• Ethambutol inhibits **arabinosyl transferase** — an enzyme important for the synthesis of the **mycobacterial cell wall**.
• Ethambutol is used in combination with pyrazinamide, isoniazid, and rifampin pending culture and susceptibility data.
• Ethambutol is well distributed throughout the body.
• Both the parent drug and metabolites are primarily **excreted in the urine**.
• The most important adverse effect is **optic neuritis**, which results in diminished visual acuity and loss of ability to discriminate between red and green.
  ✓ The risk of optic neuritis increases with **higher doses** and in patients with renal impairment.
  ✓ **Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter.**
  ✓ **Uric acid excretion is decreased** by ethambutol, and caution should be exercised in patients with **gout**.
DRUGS USED TO TREAT TUBERCULOSIS
(2nd line)
Aminoglycosides
Aminosalicylic acid PASER
Bedaquiline SIRTURO
Capreomycin CAPASTAT
Cycloserine SEROMYCIN
Ethionamide TRECATOR
Fluoroquinolones
Macrolides
<table>
<thead>
<tr>
<th>DRUG</th>
<th>ADVERSE EFFECTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>GI intolerance, tendonitis, CNS toxicity including caffeine-like effects</td>
<td>Monitor LFTs, serum creatinine / BUN, QT interval prolongation. Avoid concomitant ingestion with antacids, multivitamins or drugs containing di- or trivalent cations.</td>
</tr>
<tr>
<td>Aminoglycosides, Capreomycin</td>
<td>Nephrotoxicity, ototoxicity</td>
<td>Not available orally. Monitor for vestibular, auditory and renal toxicity.</td>
</tr>
<tr>
<td>Macrolides</td>
<td>GI intolerance, tinnitus</td>
<td>Monitor LFTs, serum creatinine / BUN, QT interval prolongation. Monitor for drug interactions due to CYP inhibition (except azithromycin).</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>GI intolerance, hepatotoxicity, hypothyroidism</td>
<td>Monitor LFTs, TSH. A majority of patients experience GI intolerance. Cross-resistance with isoniazid is possible.</td>
</tr>
<tr>
<td>Para-aminosalicylic acid (PAS)</td>
<td>GI intolerance, hepatotoxicity, hypothyroidism</td>
<td>Monitor LFTs, TSH. Patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency are at increased risk of hemolytic anemia.</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>CNS toxicity</td>
<td>Close monitoring is needed for depression, anxiety, confusion, etc. Seizures may be exacerbated in patients with epilepsy. Monitor serum creatinine.</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; CNS = central nervous system; GI = gastrointestinal; LFTs = liver function tests; TSH = thyroid-stimulating hormone