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 (MYAMBUTOL)
- Isoniazid
- Pyrazinamide
- Rifabutin (MYCOBUTIN)
- Rifampin (RIFADIN)
- Rifapentine (PRIFTIN)

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

- Aminoglycosides
- Aminosalicylic acid (PASER)
- Bedaquiline (SIRTURO)
- Capreomycin (CAPASTAT)
- Cycloserine (SEROMYCIN)
- Ethionamide (TRECATOR)
- 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.
• Patient adherence can be low when multidrug regimens last for 6 months or longer.
• One successful strategy for achieving better treatment completion rates is **directly observed therapy (DOT)**.
• Patients take their medications while being watched by a member of the health care team.
• DOT has been shown to decrease drug resistance and to improve cure rates.
• 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.
    o **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.
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<tr>
<th>Drugs Used to Treat Tuberculosis (2nd line)</th>
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BUN = blood urea nitrogen; CNS = central nervous system; GI = gastrointestinal; LFTs = liver function tests; TSH = thyroid-stimulating hormone