Antimycobacterial Drugs

I. OVERVIEW

- Mycobacteria are rod-shaped aerobic bacilli that 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.
- Mycobacterium tuberculosis can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB).

- [Note: 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 (roughly 10 million are in the United States).

- Increasing in frequency are diseases caused by non tuberculosis mycobacteria (NTM).

- These species include M. avium-intracellulare, M. chelonae, M. abscessus,
- M. kansasii, and M. fortuitum. Finally, M. leprae causes leprosy.

- 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.
- No drugs are specifically developed for NTM infections.
- Macrolides, rifamycins, and aminoglycosides are frequently included, but NTM regimens vary widely by organism.

II. CHEMOTHERAPY FOR 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, while treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years.

A. 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.

Figure 41.2 shows that resistance develops rapidly in patients given only *streptomycin*.

Multidrug therapy is employed to suppress these resistant organisms.

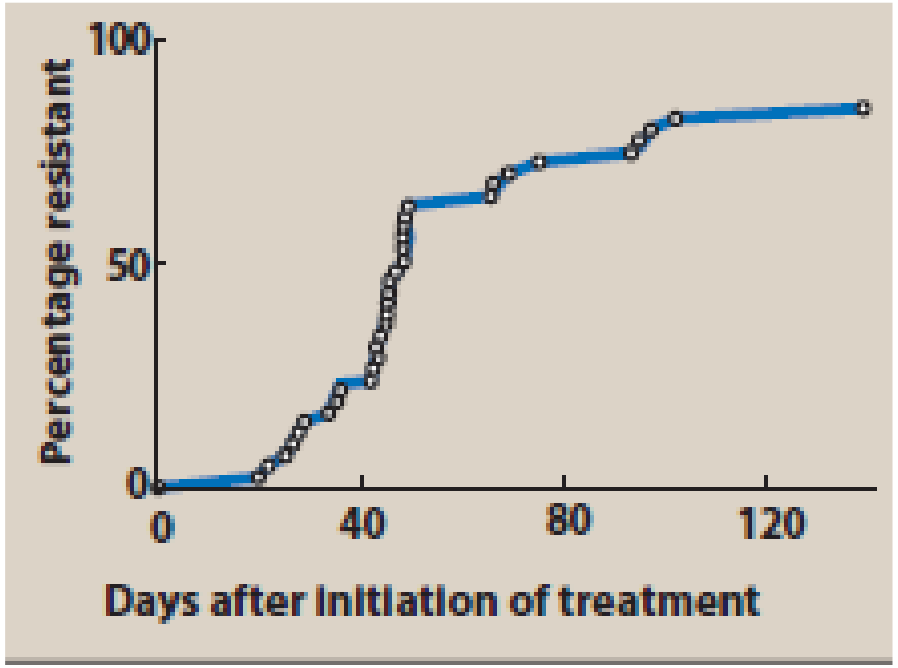


Figure 41.2
Cumulative percentage of strains of Mycobacterium tuberculosis showing resistance to *streptomycin*.

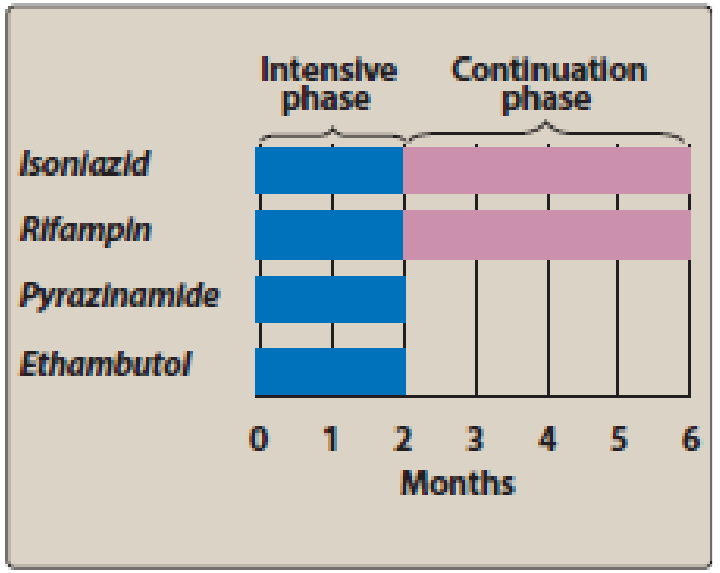
- The first-line drugs:
  - *isoniazid*,
  - *rifampin*,
  - *ethambutol*, and
  - *pyrazinamide* are preferred because of their high efficacy and acceptable incidence of toxicity.

- *Rifabutin* or *rifapentine* may replace *rifampin* under certain circumstances.

- 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.

- 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; Figure 41.3).



- Once susceptibility data are available, the drug regimen can be individually tailored.

- Second line 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),
  - a 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*.

- For extensively drug resistant TB (XDR-TB),
  - *clofazimine*,
  - *linezolid*, and other drugs may be employed empirically.

- 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, also known as 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.

B. Isoniazid

- **1. 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.

- **2. Antibacterial spectrum:**
- *Isoniazid* is specific for treatment of M. tuberculosis, although M. kansasii may be susceptible at higher drug concentrations.
- Most NTM are resistant to *INH*.
- The drug is particularly effective against rapidly growing bacilli and is also active against intracellular organisms.

- **3. Resistance:**
- Resistance follows chromosomal mutations, including
  - 1) mutation or deletion of KatG (producing mutants incapable of prodrug activation),
  - 2) varying mutations of the acyl carrier proteins, or
  - 3) overexpression of the target enzyme InhA.

- Cross resistance may occur between *isoniazid* and *ethionamide*.

- **4. 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, cells, and caseous material (necrotic tissue resembling cheese that is produced in tuberculous lesions).
- Drug concentrations in the cerebrospinal fluid (CSF) are similar to those in the serum.

- *Isoniazid* undergoes *N*-acetylation and hydrolysis, resulting in inactive products.

- [Note: *Isoniazid* acetylation is genetically regulated, with the fast acetylators exhibiting a 90-minute serum half-life, as compared to 3 to 4 hours for slow acetylators

- Excretion is through glomerular filtration and secretion, predominantly as metabolites

- Slow acetylators excrete more of the parent compound.

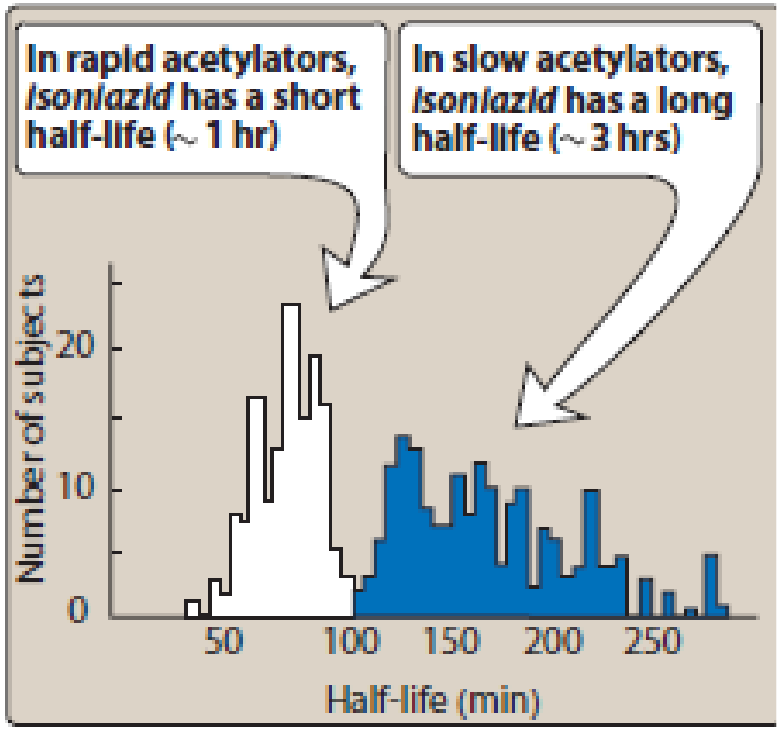


Figure 41.4
Bimodal distribution of *isoniazid* half-lives caused by rapid and slow acetylation of the drug.

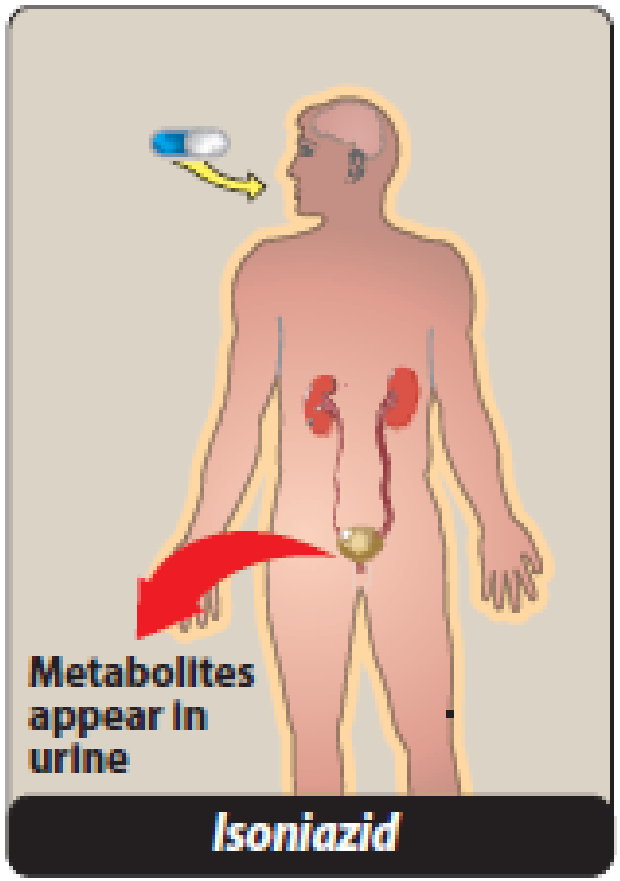


Figure 41.5
Administration and fate of *isoniazid*.

- **5. Adverse effects:**
- Hepatitis is the most serious adverse effect associated with *isoniazid*., it can be fatal.
  - The incidence increases with age (greater than 35 years old), among patients who also take *rifampin*, or among those who drink alcohol daily.

- 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.

- Because *isoniazid* inhibits the metabolism of *carbamazepine* and *phenytoin* *isoniazid* can potentiate the adverse effects of these drugs (for example, nystagmus and ataxia).

C. Rifamycins

- **rifampin,**
- **rifabutin, and**
- **rifapentine**

- macrocyclic antibiotics,

- first-line oral agents for tuberculosis.

1. Rifampin:

- has broader antimicrobial activity than *isoniazid* .

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

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

- **b. Antimicrobial spectrum:**
- bactericidal for both intracellular and extracellular mycobacteria, including
  - M. tuberculosis, and
  - NTM, such as M. kansasii and Mycobacterium avium complex (MAC).

- It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis caused by meningococci or Haemophilus influenzae.

- *Rifampin* also is highly active against M. leprae.

- **c. Resistance:**
- Resistance to *rifampin* is caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.

d. 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.
- The drug is taken up by the liver and undergoes enterohepatic recycling.

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

- Unrelated to its effects on cytochrome P450 enzymes, *rifampin* undergoes autoinduction, leading to a shortened elimination half-life over the first 1 to 2 weeks of dosing.

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

- [Note: Urine, feces, and other secretions have an orange-red color, so patients should be forewarned. Tears may even stain soft contact lenses orange-red.]

- **e. Adverse effects:**
- *Rifampin* is generally well tolerated.
- The most common adverse reactions include nausea, vomiting, and rash.

- Hepatitis and death due to liver failure are rare.
  - should be used cautiously in older patients, alcoholics, or those with chronic liver disease.

- There is a modest increase in the incidence of hepatic dysfunction when *rifampin* is coadministered with *isoniazid*.

- When *rifampin* is dosed intermittently, especially with doses of 1.2 g or greater, a flu-like syndrome can occur, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.

- **f. Drug interactions:**
- Because *rifampin* induces a number of phase I cytochrome P450 enzymes and phase II enzymes it can decrease the half-lives of coadministered drugs that are metabolized by these enzymes

- This may necessitate
  - higher dosages for coadministered drugs,
  - a switch to drugs less affected by *rifampin*, or
  - replacement of *rifampin* with *rifabutin*.

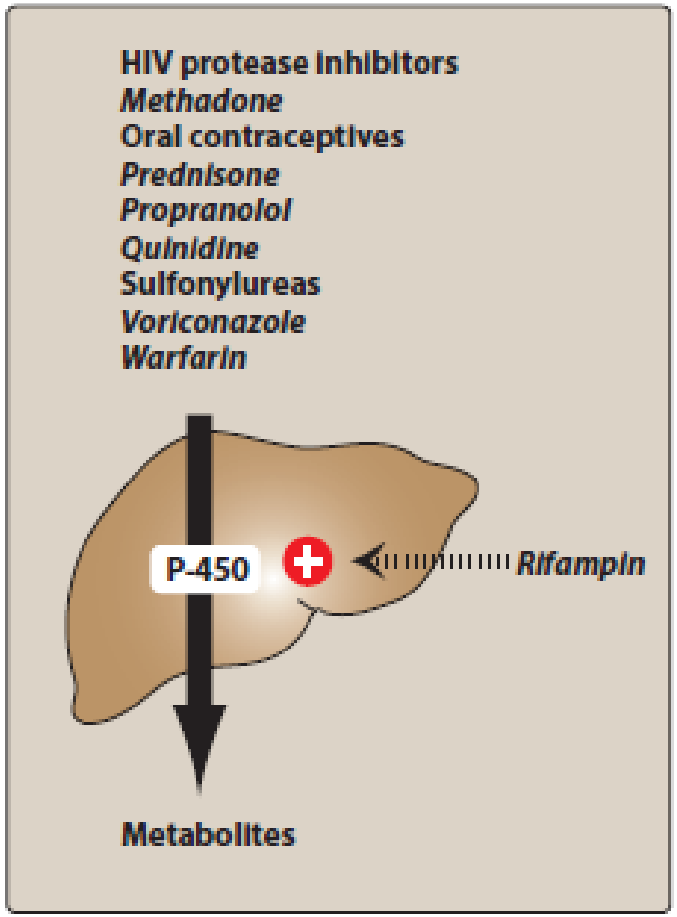


Figure 41.8
Induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system.

2. Rifabutin:

- a derivative of *rifampin*, is preferred for TB patients coinfected with the human immunodeficiency virus (HIV) who are receiving protease inhibitors (PIs) or several of the non-nucleoside reverse transcriptase inhibitors (NNRTIs).

- *Rifabutin* is a less potent inducer (approximately 40% less) of cytochrome P450 enzymes, thus lessening certain drug interactions.

- *Rifabutin* has adverse effects similar to those of *rifampin* but can also cause uveitis, skin hyperpigmentation, and neutropenia.

3. Rifapentine:

- has activity greater than that of *rifampin* in animal and in vitro studies, and it also has a longer half-life.

- In combination with *isoniazid*, *rifapentine* may be used once weekly in patients with LTBI and in select HIV-negative patients with minimal pulmonary TB.

D. Pyrazinamide

- *Pyrazinamide* [peer-a-ZIN-a-mide] 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.

- *Pyrazinamide* is active against tuberculosis bacilli in acidic lesions and in macrophages.
  - PH drops in lesions caused by TB infections.
- 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.

E. Ethambutol

- 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.
- [Note: *Ethambutol* may be discontinued if the isolate is determined to be susceptible to *isoniazid*, *rifampin*, and *pyrazinamide*.]

Ethambutol is well distributed throughout the body.

Penetration into the CNS is minimal, and it is questionably adequate for tuberculous meningitis.

- 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.

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
Isoniazid	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with *phenytoin* and *carbamazepine*.
Pyrazinamide	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
Rifampin	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

F. Alternate second-line drugs

- *Streptomycin*
- *para-aminosalicylic acid,*
- *capreomycin*
- *cycloserine*
- *ethionamide*
- fluoroquinolones,
- macrolides

- are second-line TB drugs. In general, these agents are less effective and more toxic than the first-line agents.

1. Streptomycin:

- *Streptomycin*, an aminoglycoside antibiotic, was one of the first effective agents for TB.

- Its action appears to be greater against extracellular organisms.

- Infections due to *streptomycin*-resistant organisms may be treated with *kanamycin* or *amikacin*, to which these bacilli usually remain susceptible.

2. Para-aminosalicylic acid

- *Para-aminosalicylic acid* (*PAS*) was another one of the original TB medications.

- From the early 1950s until well into the 1960s, *isoniazid*, *PAS*, plus *streptomycin* was the standard 18-month treatment regimen.

- While largely replaced by *ethambutol* for drug-susceptible TB, *PAS* remains an important component of many regimens for MDR-TB.

3. Capreomycin:

- This is a parenterally administered polypeptide that inhibits protein synthesis.
- *Capreomycin* is primarily reserved for the treatment of MDR-TB.
- Careful monitoring is necessary to minimize nephrotoxicity and ototoxicity.

4. Cycloserine:

- This is an orally effective, tuberculostatic drug that disrupts d-alanine incorporation into the bacterial cell wall.
- It distributes well throughout body fluids, including the CSF.
- *Cycloserine* is primarily excreted unchanged in urine.
- Accumulation occurs with renal insufficiency.
- Adverse effects involve CNS disturbances (for example, lethargy, difficulty concentrating, anxiety, and suicidal tendency), and seizures may occur.

5. Ethionamide:

- This is a structural analog of *isoniazid* that also disrupts mycolic acid synthesis.
- The mechanism of action is not identical to *isoniazid*, but there is some overlap in the resistance patterns.
- *Ethionamide* is widely distributed throughout the body, including the CSF.
- Metabolism is extensive, most likely in the liver, to active and inactive metabolites.
- Adverse effects that limit its use include nausea, vomiting, and hepatotoxicity.
- Hypothyroidism, gynecomastia, alopecia, impotence, and CNS effects also have been reported.

6. Fluoroquinolones:

- The fluoroquinolones, specifically *moxifloxacin* and *levofloxacin*, have an important place in the treatment of multidrug-resistant tuberculosis.

- Some NTM also are susceptible.

7. Macrolides:

- The macrolides *azithromycin* and *clarithromycin* are included in regimens for several NTM infections, including MAC.

- *Azithromycin* may be preferred for patients at greater risk for drug interactions

- (*clarithromycin* is a both a substrate and inhibitor of cytochrome P450 enzymes).

8. Bedaquiline

- **:** *Bedaquiline* an ATP synthase inhibitor, is the first in a new class of drugs approved for the treatment of MDR-TB.

- *Bedaquiline* is administered orally, and it is active against many types of mycobacteria.

- *Bedaquiline* may cause QT prolongation, and monitoring of the electrocardiogram is recommended.

- This agent is a CYP3A4 substrate, and administration with strong CYP3A4 inducers (for example, *rifampin*) should be avoided.

DRUG	ADVERSE EFFECTS	COMMENTS
Fluoroquinolones	**GI intolerance, tendonitis, CNS toxicity including caffeine-like effects**	**Monitor LFTs, serum creatinine / BUN, QT interval prolongation. Avoid concomitant ingestion with antacids, multivitamins or drugs containing di- or trivalent cations.**
Aminoglycosides, Capreomycin	**Nephrotoxicity, ototoxicity**	**Not available orally. Monitor for vestibular, auditory and renal toxicity.**
Macrolides	**GI intolerance, tinnitus**	**Monitor LFTs, serum creatinine / BUN, QT interval prolongation. Monitor for drug interactions due to CYP inhibition (except *azithromycin*).**
Ethionamide	**GI intolerance, hepatotoxicity, hypothyroidism**	**Monitor LFTs, TSH. A majority of patients experience GI intolerance. Cross-resistance with *isoniazid* is possible.**
Para-aminosalicylic acid (PAS)	**GI intolerance, hepatotoxicity, hypothyroidism**	**Monitor LFTs, TSH. Patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency are at increased risk of hemolytic anemia.**
Cycloserine	**CNS toxicity**	**Close monitoring is needed for depression, anxiety, confusion, etc. Seizures may be exacerbated in patients with epilepsy. Monitor serum creatinine.**

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

III. DRUGS FOR LEPROSY

- Leprosy (or Hansen's disease) is uncommon in the United States;
- however, worldwide it is a much larger problem.
- Leprosy can be treated effectively with *dapsone* and *rifampin*, adding *clofazimine* in multibacillary cases.

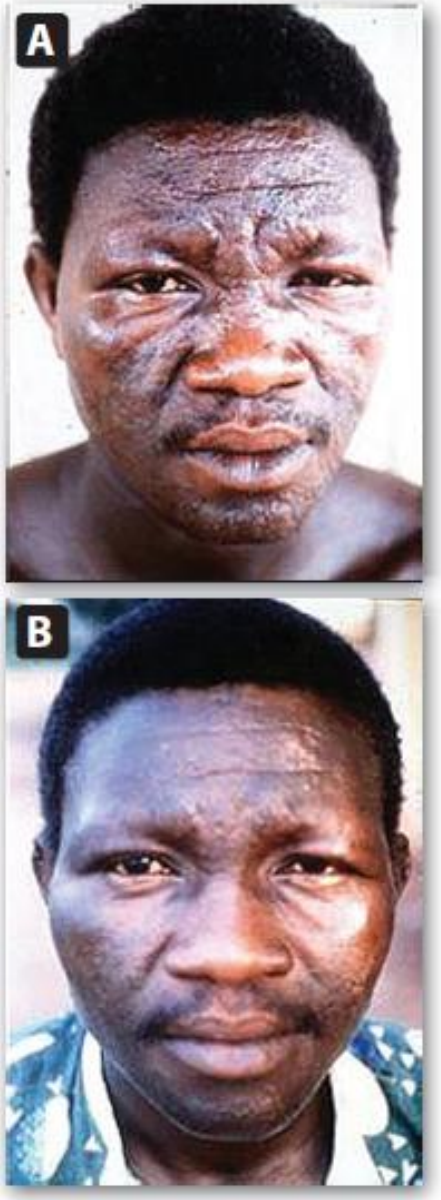


Figure 41.12
Leprosy patient. **A.** Before therapy. **B.** After 6 months of multidrug therapy.

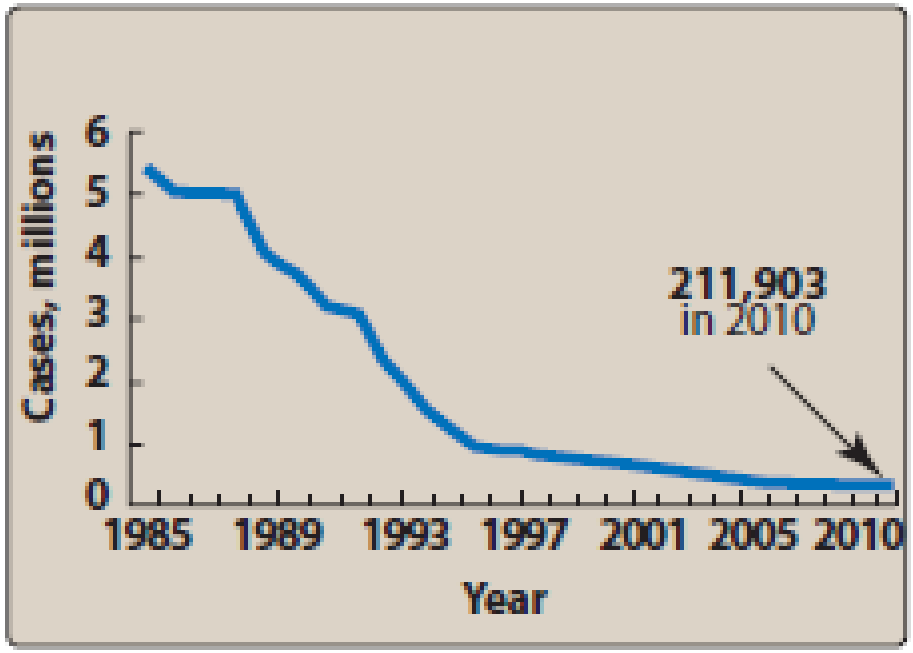


Figure 41.11
Reported prevalence of leprosy worldwide.

A. Dapsone

- *Dapsone* [DAP-sone] is structurally related to the sulfonamides and similarly inhibits dihydropteroate synthetase in the folate synthesis pathway.

It is bacteriostatic for M. leprae, and resistant strains may be encountered.

Dapsone also is used in the treatment of pneumonia caused by Pneumocystis jirovecii in immunosuppressed patients.

- The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high concentrations in the skin.
- The parent drug undergoes hepatic acetylation.
- Both parent drug and metabolites are eliminated in the urine.
- Adverse reactions include hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and peripheral neuropathy.

B. Clofazimine

- Its mechanism of action may involve binding to DNA, although alternative mechanisms have been proposed.

Its redox properties may lead to the generation of cytotoxic oxygen radicals that are toxic to the bacteria.

Clofazimine is bactericidal to M. leprae, and it has potentially useful activity against M. tuberculosis and NTM.

Following oral absorption, the drug accumulates in tissues, allowing intermittent therapy but does not enter the CNS.

Patients typically develop a pink to brownish-black discoloration of the skin and should be informed of this in advance.

Eosinophilic and other forms of enteritis, sometimes requiring surgery, have been reported.

Clofazimine has some anti-inflammatory and anti-immune activities. Thus, erythema nodosum leprosum may not develop in patients treated with this drug.

- 41.1 A 35-year-old male, formerly a heroin abuser, has been on methadone maintenance for the last 13 months. Two weeks ago, he had a positive tuberculosis skin test (PPD test), and a chest radiograph showed evidence of right upper lobe infection. He was started on standard four-drug antimycobacterial therapy. He has come to the emergency department complaining of “withdrawal symptoms.” Which of the following antimycobacterial drugs is likely to have caused this patient’s acute withdrawal reaction?
- A. Ethambutol.
- B. Isoniazid.
- C. Pyrazinamide.
- D. Rifampin.
- E. Streptomycin.

- 41.2 A 42-year-old male HIV patient was recently diagnosed with active tuberculosis. Currently, he is on a stable HIV regimen consisting of two protease inhibitors and two nucleoside reverse transcriptase inhibitors (NRTIs). What is the most appropriate regimen to use for treatment of his tuberculosis?
- A. Rifampin + isoniazid + pyrazinamide + ethambutol.
- B. Rifabutin + isoniazid + pyrazinamide + ethambutol.
- C. Rifapentine + isoniazid + pyrazinamide + ethambutol.
- D. Rifampin + moxifloxacin + pyrazinamide + ethambutol.
- E. Amikacin + moxifloxacin + cycloserine + streptomycin.

- 41.3 Which of the following is correct regarding clofazimine in the treatment of leprosy?

- A. Clofazimine should not be used in patients with a deficiency in glucose-6-phosphate dehydrogenase (G6PD).
- B. Peripheral neuropathy is one of the most common adverse effects seen with the drug.
- C. Clofazimine may cause skin discoloration over time.
- D. The risk of erythema nodosum leprosum is increased in patients given clofazimine.

- 41.4 A 24-year-old male has returned to the clinic for his 1-month check-up after starting treatment for tuberculosis. He is receiving isoniazid, rifampin, pyrazinamide, and ethambutol. He states he feels fine, but now is having difficulty reading his morning newspaper and feels he may need to get glasses. Which of the following drugs may be causing his decline in vision?
- A. Isoniazid.
- B. Rifampin.
- C. Pyrazinamide.
- D. Ethambutol.