**Antimycobacterials**

**I. OVERVIEW**

Mycobacteria are slender, rod-shaped bacteria with lipid-rich cell walls that stain poorly with the Gram stain, but once stained, the walls cannot be easily decolorized by treatment with acidified organic solvents. Hence, they are termed “acid-fast.” The most widely encountered mycobacterial infection is tuberculosis—the leading cause worldwide of death from infection. Members of the genus Mycobacterium also cause leprosy, as well as, several tuberculosis-like human infections. Mycobacterial infections are intracellular and, generally, result in the formation of slow-growing granulomatous lesions that are responsible for major tissue destruction. Diagnostic testing for tuberculosis can be accomplished via the standard tuberculin skin test with purified protein derivative (PPD) or by an interferon-gamma release assay (IGRA) blood test, Quantiferon-TB Gold, approved by the FDA in 2005. The advantages that the blood test offers is that it requires only a single test visit, and it is less susceptible to false- positive results due to BCG vaccination or to infection with mycobacteria other than Mycobacterium tuberculosis. However, the cost of the blood test is more than that of the skin test, yet it reduces the expense of fol- low-up x-rays and lab tests needed with a tuberculin skin test. There are four currently recommended first-line agents utilized for antituberculosis therapy (Figure 34.1). Second-line medications are either less effective, more toxic, or have not been studied as extensively. They are useful in patients who cannot tolerate the first-line drugs or who are infected with myobacteria that are resistant to the first-line agents.

**II. CHEMOTHERAPY FOR TUBERCULOSIS**

Mycobacterium tuberculosis, one of a number of mycobacteria, can lead to serious infections of the lungs, genitourinary tract, skeleton, and meninges. Treating tuberculosis as well as other mycobacterial infections presents therapeutic problems. The organism grows slowly; thus, are difficult to culture and may have to be treated for 6 months to 2 years. Resistant organisms readily emerge, particularly in patients who have had prior therapy or who fail to adhere to the treatment protocol. It is currently estimated that about one-third of the world’s population is infected with M. tuberculosis, with 30 million people having active disease. Worldwide, 9 million new cases occur, and approximately 2 million people die of the disease each year.

1. **Strategies for addressing drug resistance**

Strains of M. tuberculosis that are resistant to a particular agent emerge during treatment with a single drug. For example, Figure 34.2 shows that resistance rapidly develops in patients given only streptomycin. Therefore, multidrug therapy is employed when treating tuberculosis in an effort to delay or prevent the emergence of resistant strains. Isoniazid, rifampin (or rifabutin or rifapentine), ethambutol, and pyrazin amide are the principal or so-called “first-line” drugs because of their efficacy and acceptable degree of toxicity. Today, however, because of poor patient compliance and other factors, the number of multidrug-resistant organ- isms has risen. Some bacteria have been identified that are resistant to as many as seven antitubercular agents. Therefore, although treatment regimens vary in duration and in the agents employed, they always include a minimum of two drugs, preferably with both being bactericidal (see p. 370) The combination of drugs should prevent the emergence of resistant strains. The multi drug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms. For example, the initial short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months and then isoniazid and rifampin for the next 4 months (the “continuation phase”; Figure 34.3). Before susceptibility data are available, more drugs may be added to the first-line agents for patients who have previously had tuberculosis or those in whom multidrug-resistant tuberculosis is suspected. The added drugs normally include an aminoglycoside (strep- tomycin, kanamycin, or amikacin) or capreomycin (injectable agents), a fluoroquinolone, and perhaps a second-line anti tuberculosis agent such as cycloserine, ethionamide, or p-aminosalicylic acid. Once susceptibility data are available, the drug regimen can be individually tailored to the patient. Patient compliance is often low when multidrug schedules last for 6 months or longer. One successful strategy for achieving better treatment completion rates is “directly observed therapy,” also known as DOT, in which patients take their medication while being supervised and observed. DOT has been shown to decrease drug resistance as well as relapse and mortality rates and to improve cure rates. Most local and state health departments offer DOT services.

1. **Isoniazid**

Isoniazid [eye-soe-NYE-a-zid], the hydrazide of isonicotinic acid, is a synthetic analog of pyridoxine. It is the most potent of the antitubercular drugs, but is never given as a single agent in the treatment of active tuberculosis. Its introduction revolutionized the treatment of tuberculosis.

**1. Mechanism of action**: Isoniazid, often referred to as INH, is a pro- drug that is activated by a mycobacterial catalase-peroxidase (KatG). Genetic and biochemical evidence has implicated at least two different target enzymes for isoniazid within the unique Type II fatty acid synthase system involved in the production of mycolic acids. [Note: Mycolic acid is a unique class of very-long-chain, β-hydroxylated fatty acids found in mycobacterial cell walls. Decreased mycolic acid synthesis corresponds with the loss of acid-fastness after expo- sure to isoniazid.] The targeted enzymes are enoylacyl carrier protein reductase (InhA) and a β-ketoacyl-ACP synthase (KasA). The activated drug covalently binds to and inhibits these enzymes, which are essential for the synthesis of mycolic acid.

**2. Antibacterial spectrum**: For bacilli in the stationary phase, isoniazid is bacteriostatic, but for rapidly dividing organisms, it is bacteriidal. It is effective against intracellular bacteria. Isoniazid is specific for treatment of M. tuberculosis, although Mycobacterium kansasii (an organism that causes three percent of the clinical illness known as tuberculosis) may be susceptible at higher drug levels. When it is used alone, resistant organisms rapidly emerge.

**3. Resistance**: This is associated with several different chromosomal mutations, each of which results in one of the following: mutation or deletion of KatG (producing mutants incapable of prodrug activation), varying mutations of the acyl carrier proteins, or over expres- sion of InhA. Cross-resistance does not occur between isoniazid and other antitubercular drugs.

**4. Pharmacokinetics**: Orally administered isoniazid is readily absorbed. Absorption is impaired if isoniazid is taken with food, particularly carbohydrates, or with aluminum-containing antacids. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tubercles). Drug levels in the cerebrospinal fluid (CSF) are about the same as those in the serum. The drug readily penetrates host cells and is effective against bacilli growing intracellularly. Infected tissue tends to retain the drug lon ger. Isoniazid undergoes N-acetylation and hydrolysis, resulting in inactive products. [Note: Acetylation is genetically regulated, with the fast acetylator trait being autosomally dominant. A bimodal distribution of fast and slow acetylators exists (Figure 34.4).] Chronic liver disease decreases metabolism, and doses must be reduced. Excretion is through glomerular filtration, predominantly as metabolites (Figure 34.5). Slow acetylators excrete more of the parent com- pound. Severely depressed renal function results in accumulation of the drug, primarily in slow acetylators.

**5. Adverse effects**: The incidence of adverse effects is fairly low. Except for hypersensitivity, adverse effects are related to the dosage and duration of administration.

**a. Peripheral neuritis**: Peripheral neuritis (manifesting as paresthesias of the hands and feet), which is the most common adverse effect, appears to be due to a relative pyridoxine deficiency. Most of the toxic reactions are corrected by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B6). [Note: Isoniazid can achieve levels in breast milk that are high enough to cause a pyridoxine defciency in the infant unless the mother is supplemented with the vitamin.]

**b. Hepatitis and idiosyncratic hepatotoxicity**: Potentially fatal hepatitis is the most severe side effect associated with isoniazid. It has been suggested that this is caused by a toxic metabolite of monoacetylhydrazine, formed during the metabolism of isoniazid. The incidence increases among patients with increasing age, among patients who also take rifampin, or among those who drink alcohol daily.

**c. Drug interactions:** Because isoniazid inhibits metabolism of phenytoin (Figure 34.6), isoniazid can potentiate the adverse effects of that drug (for example, nystagmus and ataxia). Slow acetylators are particularly at risk.

**d. Other adverse effects**: Mental abnormalities, convulsions in patients prone to seizures, and optic neuritis have been observed. Hypersensitivity reactions include rashes and fever.

**C. Rifamycins**: **Rifampin, rifabutin and rifapentine**

Rifampin, rifabutin, and rifapentine are all considered to be rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line drugs for tuberculosis. Any of these rifamycins must always be used in conjunction with at least one other antituberculosis drug to which the isolate is susceptible.

**1. Rifampin**: Rifampin [rif-AM-pin], which is derived from the soil mold Strepto myces, has a broader antimicrobial activity than isoniazid and has found application in the treatment of a number of different bacterial infections. Because resistant strains rapidly emerge during therapy, it is never given as a single agent in the treatment of active tuberculosis.

a**. Mechanism of action**: Rifampin blocks transcription by interacting with the β subunit of bacterial, but not human, DNA- dependent RNA polymerase. [Note: The drug is thus specific for prokaryotes.] Rifampin inhibits mRNA synthesis by suppressing the initiation step.

**b. Antimicrobial spectrum**: Rifampin is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and atypical mycobacteria, such as M. kansasii. 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 is the most active antileprosy drug at present, but to delay the emergence of resistant strains, it is usually given in combination with other drugs. Rifabutin, an analog of rifampin, has some activity against Mycobacterium avium-intracellulare complex, but is less active against tuberculosis.

**c. Resistance**: Resistance to rifampin can be caused by a mutation in the affinity of the bacterial DNA-dependent RNA polymerase for the drug, or by decreased permeability.

d**. Pharmacokinetics**: Absorption is adequate after oral administration. Distribution of rifampin occurs to all body fluids and organs. Adequate levels are attained in the CSF even in the absence of inflammation. The drug is taken up by the liver and undergoes enterohepatic cycling. Rifampin itself can induce the hepatic mixed-function oxidases (see p. 14), leading to a shortened half-life and numerous drug interactions. Elimination of metabolites and the parent drug is via the bile into the feces or via the urine (Figure 34.7). [Note: Urine and feces, as well as, other secretions have an orange-red color; patients should be forewarned. Tears may permanently 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 is rare; however, the drug should be used judiciously in patients who are alcoholic, elderly, or have chronic liver disease due to the increased incidence of severe hepatic dysfunction when rifampin is administered alone or concomitantly with isoniazid. Often, when rifampin is dosed intermittently, or in daily doses of 1.2 grams or greater, a flu-like syndrome is associated with fever, chills, and myalgias and sometimes is associated with acute renal failure, hemolytic anemia, and shock.

**f. Drug interactions**: Because rifampin can induce a number of cytochrome P450 enzymes (see p. 14), it can decrease the half- lives of other drugs that are co-administered and metabolized by this system (Figure 34.8). This may lead to higher dosage requirements for these agents.

**2. Rifabutin:** Rifabutin [rif-a-BYOO-tin], a derivative of rifampin, is the preferred drug for use in tuberculosis-infected patients with the human immunodeficiency virus (HIV), who are concomitantly treated with protease inhibitors or nonnucleoside reverse tran- scriptase inhibitors, because it is a less potent inducer of cytochrome P450 enzymes. Rifabutin has adverse effects similar to those of rifampin, but can also cause uveitis, skin hyperpigmentation, and neutropenia.

**3. Rifapentine**: Rifapentine [rih-fa-PEN-teen] has activity comparable to that of rifampin but has a longer half-life than rifampin and rifabutin, which permits weekly dosing. However, for the intensive phase (initial 2 months) of the short-course therapy for tuberculosis, rifapentine is given twice weekly. In the subsequent phase, rifapentine is dosed once per week for 4 months. To avoid resistance issues, rifap- entine should not be used alone but, rather, be included in a three to four-drug regimen.

**D. Pyrazinamide**

Pyrazinamide [peer-a-ZIN-a-mide] is a synthetic, orally effective, bactericidal, antitubercular agent used in combination with isoniazid, rifampin, and ethambutol. It is bactericidal to actively dividing organisms, but the mechanism of its action is unknown. Pyrazinamide must be enzymatically hydrolyzed to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase. Pyrazinamide is active against tubercle bacilli in the acidic environment of lysosomes, as well as, in macrophages. Pyrazinamide distributes throughout the body, penetrating the CSF. It undergoes extensive metabolism. About one to five percent of patients taking isoniazid, rifampin, and pyrazin amide may experience liver dysfunction. Urate retention can also occur, and may precipitate a gouty attack (Figure 34.9).

**E. Ethambutol**

Ethambutol [e-THAM-byoo-tole] is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii. Ethambutol inhibits arabinosyl transferase—an enzyme that is important for the synthesis of the mycobacterial arabinogalactan cell wall. Resistance is not a serious problem if the drug is employed with other antitubercular agents. Ethambutol can be used in combination with pyrazinamide, isoniazid, and rifampin to treat tuberculosis. Absorbed on oral administration, ethambutol is well distributed throughout the body. Penetration into the central nervous system (CNS) is therapeutically adequate in tuber-culous meningitis. Both parent drug and metabolites are excreted by glomerular filtration and tubular secretion. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. Visual acuity should be periodically examined. Discontinuation of the drug results in reversal of the optic symptoms. In addition, urate excretion is decreased by the drug; thus, gout may be exacerbated (see Figure 34.9). Figure 34.10 summarizes some of the characteristics of first-line drugs.

**F. Alternate second-line drugs**

A number of drugs—streptomycin, [strep-toe-MY-sin], para-aminosalicylic acid [a-mee-noe-sal-i-SIL-ik], ethionamide [e-thye-ON-am-ide], cycloserine [sye-kloe-SER-een], capreomycin [kap-ree-oh-MYE sin], fluo- roquinolones, and macrolides—are considered to be second-line drugs, either because they are no more effective than the first-line agents and their toxicities are often more serious, or because they are particularly active against atypical strains of mycobacteria.

**1. Streptomycin**: This is the first antibiotic effective in the treatment of tuberculosis and is discussed with the aminoglycosides (see p. 399). Its action is directed against extracellular organisms. Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin, to which these bacilli remain sensitive.

**2. Capreomycin**: This is a peptide that inhibits protein synthesis. It is administered parenterally. Capreomycin is primarily reserved for the treatment of multidrug-resistant tuberculosis. Careful monitoring of the patient is necessary to prevent its nephrotoxicity and ototoxicity.

**3. Cycloserine** is an orally effective, tuberculostatic agent that appears to antagonize the steps in bacterial cell wall synthesis involving D-alanine. It distributes well throughout body fluids, including the CSF. Cycloserine is metabolized, and both parent and metabolite are excreted in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances, and epileptic seizure activity may be exacerbated. Peripheral neuropathies are also a problem, but they respond to pyridoxine.

**4. Ethionamide**: This is a structural analog of isoniazid, but it is not believed to act by the same mechanism. Ethionamide can inhibit acetylation of isoniazid (Figure 34.11). It is effective after oral administration and is widely distributed throughout the body, including the CSF. Metabolism is extensive, and the urine is the main route of excretion. Adverse eff ects that limit its use include gastric irritation, hepatotoxicity, peripheral neuropathies, and optic neuritis. Supplementation with vitamin B6 (pyridoxine) may lessen the sever- ity of neurologic side effects.

**5. Fluoroquinolones**: The fluoroquinolones, specifi cally, ciprofl oxacin, moxifloxacin and levofloxacin have an important place in the treatment of multidrug-resistant tuberculosis. Some atypical strains of mycobacteria are also susceptible. These drugs are discussed in detail in Chapter 33.

**6. Macrolides**: The macrolides, such as azithromycin and clarithromycin, are part of the regimen that includes ethambutol and rifabutin used for the treatment of infections by M. avium-intracellulare complex. Azithromycin is preferred for HIV-infected patients because it is least likely to interfere with the metabolism of antiretroviral drugs. Details about the pharmacology of macrolides are found in Chapter 32.

**III. CHEMOTHERAPY FOR LEPROSY**

Leprosy (or, as it is specified by the U.S. Public Health Service, Hansen’s dis- ease) is rare in the United States, but a small number of cases, both imported and domestically acquired, are reported each year. Worldwide, it is a much larger problem (Figure 34.12). Approximately 70 percent of all cases in the world are located in India. Bacilli from skin lesions or nasal discharges of infected patients enter susceptible individuals via abraded skin or the respi- ratory tract. The World Health Organization recommends the triple-drug regimen of dapsone, clofazimine, and rifampin for 6 to 24 months. Figure 34.13 shows the eff ects of multi-drug therapy.

1. **Dapsone**

Dapsone [DAP-sone] is structurally related to the sulfonamides and similarly inhibits folate synthesis via dihydropteroate synthetase inhibiton. It is bacteriostatic for Mycobacterium leprae, but resistant strains are encountered. Dapsone is also employed in the treatment of pneumonia caused by Pneumocystis jiroveci in patients infected with HIV. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high levels concentrated in the skin. The parent drug enters the enterohepatic circulation and undergoes hepatic acetylation. Both parent drug and metabolites are eliminated through the urine. Adverse reactions include hemolysis, especially in patients with glucose 6-phosphate dehydrogenase deficiency, as well as methemoglobinemia, peripheral neuropathy, and the possibility of developing erythema nodosum leprosum (a serious and severe skin com- plication of leprosy). [Note: The latter is treated with corticosteroids or thalidomide.]

1. **Clofazimine**

Clofazimine [kloe-FA-zi-meen] is a phenazine dye that binds to DNA and prevents it from serving as a template for future DNA replication. Its redox properties may lead to the generation of cytotoxic oxygen radicals that are also toxic to the bacteria. Clofazimine is bactericidal to M. leprae and has some activity against M. avium-intracellulare complex. Following oral absorption, the drug accumulates in tissues, allowing intermittent therapy, but it does not enter the CNS. Patients may develop a red-brown discoloration of the skin. Eosinophilic enteritis has been reported as an adverse effect. The drug also has some anti-inflammatory activity; thus, erythema nodosum leprosum does not develop.