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Drugs Used in Tuberculosis and Leprosy

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Tuberculosis remains the most important communicable disease in the world. The World Health organization (WHO) estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis*. Groups that are at high risk for tuberculosis infection include HIV-infected persons, immigrants from countries with high rates of tuberculosis, the homeless, health care professionals, intravenous drug users, persons taking immunosuppressive agents, and those in institutional settings, such as nursing homes and correctional facilities. Along with the recent increase in cases of tuberculosis, there is a progressive increase in multidrug-resistant (MDR) tuberculosis. Some of the MDR isolates are resistant to as many as seven of the commonly employed antimycobacterial drugs.

KEY CONCEPTS IN THE TREATMENT OF TUBERCULOSIS

The ability of the tubercle bacillus to remain dormant but viable and capable of causing disease is a major therapeutic challenge. The mycobacteria are slow-growing intracellular organisms that require the administration of a combination of drugs for extended periods to achieve effective therapy and to prevent the emergence of resistance. The risk of adverse reactions therefore must be a major consideration in drug selection.

The three basic concepts in tuberculosis treatment are as follows: (1) Regimens must contain multiple drugs to which the organism is susceptible. (2) Drugs must be taken regularly. (3) Drug therapy must con-

tinue for a sufficient time. Traditionally, antituberculosis drugs that are classified as *first-line* drugs are superior in efficacy and possess an acceptable degree of toxicity. These agents include isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. Most patients with tuberculosis can be treated successfully with these drugs.

Second-line drugs are more toxic and less effective, and they are indicated only when the *M. tuberculosis* organisms are resistant to the first-line agents. Therapy with second-line agents may have to be prolonged beyond the standard period of treatment, depending on the clinical, radiographic, and microbiological response to therapy. The second-line agents include cycloserine, ethionamide, aminosalicylic acid, rifabutin, quinolones, capreomycin, viomycin, and thiacetazone.

FIRST-LINE ANTITUBERCULOSIS DRUGS

Isoniazid

Isoniazid (isonicotinic acid hydrazide, or INH) is the most active drug for the treatment of tuberculosis caused by susceptible strains. It is a synthetic agent with a structural similarity to that of pyridoxine.

Mechanism of Action

Isoniazid is active against susceptible bacteria only when they are undergoing cell division. Susceptible bacteria may continue to undergo one or two divisions before multiplication is arrested. Isoniazid can inhibit the synthesis of mycolic acids, which are essential components of mycobacterial cell walls. The mycobacterial enzyme catalase–peroxidase *KatG* activates the administered isoniazid to its biologically active form. The target sites for the activated isoniazid action are acyl carrier protein AcpM and Kas A, a β -ketoacyl carrier protein synthetase that blocks mycolic acid synthesis. Isoniazid exerts its lethal effects at the target sites by forming covalent complexes.

Antimicrobial Activity

Isoniazid is bactericidal against actively growing *M. tuberculosis* and bacteriostatic against nonreplicating organisms. The minimal tuberculostatic inhibitory concentration (MIC) of isoniazid is 0.025 to 0.05 $\mu\text{g/mL}$.

Resistance

The most common mechanism of isoniazid resistance is the mycobacteria's formation of mutations in catalase–peroxidase *KatG*, the enzyme that is responsible for activation of isoniazid. Another resistance mechanism is through a missense mutation related to the *inhA* gene involved in mycolic acid biosynthesis.

An active tuberculosis cavity may contain as many as 10^7 to 10^{10} microorganisms. The frequency of isoniazid-resistant mutants in a susceptible mycobacterial population is about 1 bacillus in 10^6 , and this organism is readily selected out if isoniazid is given as the sole agent. If a second drug having a similar drug resistance (1 in 10^6) is combined with isoniazid, the odds that a bacillus is resistant to both drugs become 1 in 10^{12} . *Therefore, it is vital to combine at least two antitubercular agents to which the organism is susceptible.*

Pharmacokinetic Properties

Isoniazid is water soluble and is well absorbed when administered either orally or parenterally. Oral absorption is decreased by concurrent administration of aluminum-containing antacids.

Isoniazid does not bind to serum proteins; it diffuses readily into all body fluids and cells, including the caseous tuberculous lesions. The drug is detectable in significant quantities in pleural and ascitic fluids, as well as in saliva and skin. The concentrations in the central nervous system (CNS) and cerebrospinal fluid are generally about 20% of plasma levels but may reach close to 100% in the presence of meningeal inflammation.

Isoniazid is acetylated to acetyl isoniazid by *N*-acetyltransferase, an enzyme in liver, bowel, and kidney. Individuals who are genetically rapid acetylators will have a higher ratio of acetyl isoniazid to isoniazid than will slow acetylators. Rapid acetylators were once thought to be more prone to hepatotoxicity, but this is not proved. The slow or rapid acetylation of isoniazid is rarely important clinically, although slow inactivators tend to develop peripheral neuropathy more readily. Metabolites of isoniazid and small amounts of unaltered drug are excreted in the urine within 24 hours of administration.

Clinical Uses

Isoniazid is among the safest and most active mycobactericidal agents. It is considered the primary drug for use in all therapeutic and prophylactic regimens for susceptible tuberculosis infections. It is also included in the first-line drug combinations for use in all types of tuberculous infections. Isoniazid is preferred as a single agent in the treatment of latent tuberculosis infections in high-risk persons having a positive tuberculin skin reaction with no radiological or other clinical evidence of tuberculosis. *Mycobacterium kansasii* is usually susceptible to isoniazid, and it is included in the standard multidrug treatment regimen.

Adverse Effects

The incidence and severity of adverse reactions to isoniazid are related to dosage and duration of therapy. Isoniazid-induced hepatitis and peripheral neuropathy are two major untoward effects.

A minor asymptomatic increase in liver aminotransferase is seen in 10 to 20% of patients, whereas fatal hepatitis is seen in fewer than 1% of isoniazid recipients. Risk factors for hepatitis include underlying liver disease, advanced age, pregnancy, and combination therapy with acetaminophen. Early recognition and prompt discontinuation of the drug is recommended to prevent further damage to the liver.

Peripheral neuropathy is observed in 10 to 20% of patients taking more than 5 mg/kg/day of isoniazid. Patients with underlying chronic disorders such as alcoholism, malnutrition, diabetes, and AIDS are at particular risk for neurotoxicity; compared with fast acetylators, neurotoxicity is more frequent in slow acetylators because slow acetylators achieve higher drug plasma levels. Isoniazid promotes renal excretion of pyridoxine, resulting in a relative deficiency and neuropathy. CNS toxicity may range from excitability and seizures to psychosis. The neurotoxic effects are reversed without altering the antimycobacterial action by the administration of 10 to 50 mg/day of pyridoxine. Other adverse reactions include gastrointestinal (GI) intolerance, anemia, rash, tinnitus, and urinary retention.

Drug Interactions

High isoniazid plasma levels inhibit phenytoin metabolism and potentiate phenytoin toxicity when the two drugs are coadministered. The serum concentrations of phenytoin should be monitored, and the dose should be adjusted if necessary.

Rifampin

Mechanism of Action

Rifampin is a semisynthetic macrocyclic antibiotic produced from *Streptomyces mediterranei*. It is a large lipid-soluble molecule that is bactericidal for both intracellular and extracellular microorganisms. Rifampin binds strongly to the β -subunit of bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. Rifampin does not affect mammalian polymerases.

Antibacterial Activity and Resistance

In addition to *M. tuberculosis*, rifampin is active against *Staphylococcus aureus*, *Neisseria meningitidis*, *Haemophilus influenzae*, Chlamydiae, and certain viruses. Rifampin resistance results from a point mutation or deletion in *rpoB*, the gene for the β -subunit of RNA polymerase, thereby preventing the binding of RNA polymerase.

Pharmacokinetic Properties

Rifampin is well absorbed orally, and a peak serum concentration is usually seen within 2 to 4 hours. Drug ab-

sorption is impaired if rifampin is given concurrently with aminosalicic acid or is taken immediately after a meal. It is widely distributed throughout the body, and therapeutic levels are achieved in all body fluids, including cerebrospinal fluid. Rifampin is capable of inducing its own metabolism, so its half-life can be reduced to 2 hours within a week of continued therapy. The deacetylated form of rifampin is active and undergoes biliary excretion and enterohepatic recirculation. Most of the drug is excreted into the GI tract and a small amount in the urine. Moderate dose adjustment is required in patients with underlying liver disease.

Clinical Uses

Rifampin is a first-line antitubercular drug used in the treatment of all forms of pulmonary and extrapulmonary tuberculosis. Rifampin is an alternative to isoniazid in the treatment of latent tuberculosis infection. Rifampin also may be combined with an antileprosy agent for the treatment of leprosy and to protect those in close contact with patients having *H. influenzae* type b and *N. meningitidis* infection; rifampin is also used in methicillin-resistant staphylococcal infections, such as osteomyelitis and prosthetic valve endocarditis.

Adverse Reactions

The most commonly observed side effects are GI disturbances and nervous system symptoms, such as nausea, vomiting, headache, dizziness, and fatigue. Hepatitis is a major adverse effect, and the risk is highest in patients with underlying liver diseases and in slow isoniazid acetylators; the rate of hepatotoxicity is increased if isoniazid and rifampin are combined.

Other major untoward reactions are the result of rifampin's ability to induce hepatic cytochrome P-450 enzymes, leading to an increased metabolism of many drugs; this action has especially complicated the treatment of tuberculosis in HIV-infected patients whose regimen includes protease inhibitors and nonnucleoside reverse transcriptase. Since rifabutin has relatively little of these effects, it is commonly substituted for rifampin in the treatment of tuberculosis in HIV-infected patients.

Hypersensitivity reactions, such as pruritus, cutaneous vasculitis, and thrombocytopenia, are seen in some patients, and an immune-mediated systemic flulike syndrome with thrombocytopenia also has been described. Rifampin imparts a harmless red-orange color to urine, feces, saliva, sweat, tears, and contact lenses. Patients should be advised of such discoloration of body fluids.

Pyrazinamide

Pyrazinamide is a synthetic analogue of nicotinamide. Its exact mechanism of action is not known, although its target appears to be the mycobacterial fatty acid

synthetase involved in mycolic acid biosynthesis. Pyrazinamide requires an acidic environment, such as that found in the phagolysosomes, to express its tuberculocidal activity. Thus, pyrazinamide is highly effective on intracellular mycobacteria. The mycobacterial enzyme pyrazinamidase converts pyrazinamide to pyrazinoic acid, the active form of the drug. A mutation in the gene (*pncA*) that encodes pyrazinamidase is responsible for drug resistance; resistance can be delayed through the use of drug combination therapy.

Pyrazinamide is well absorbed from the GI tract and is widely distributed throughout the body. It penetrates tissues, macrophages, and tuberculous cavities and has excellent activity on the intracellular organisms; its plasma half-life is 9 to 10 hours in patients with normal renal function. The drug and its metabolites are excreted primarily by renal glomerular filtration.

Clinical Uses

Pyrazinamide is an essential component of the multidrug short-term therapy of tuberculosis. In combination with isoniazid and rifampin, it is active against the intracellular organisms that may cause relapse.

Adverse Reactions

Hepatotoxicity is the major concern in 15% of pyrazinamide recipients. It also can inhibit excretion of urates, resulting in hyperuricemia. Nearly all patients taking pyrazinamide develop hyperuricemia and possibly acute gouty arthritis. Other adverse effects include nausea, vomiting, anorexia, drug fever, and malaise. Pyrazinamide is not recommended for use during pregnancy.

Ethambutol

Ethambutol is a water-soluble, heat-stable compound that acts by inhibition of arabinosyl transferase enzymes that are involved in cell wall biosynthesis. Nearly all strains of *M. tuberculosis* and *M. kansasii* and most strains of *Mycobacterium avium-intracellulare* are sensitive to ethambutol. Drug resistance relates to point mutations in the gene (*EmbB*) that encodes the arabinosyl transferases that are involved in mycobacterial cell wall synthesis.

Orally administered ethambutol is well absorbed (70–80%) from the gut, and peak serum concentrations are obtained within 2 to 4 hours of administration; it has a half-life of 3 to 4 hours. Ethambutol is widely distributed in all body fluids, including the cerebrospinal fluid, even in the absence of inflammation. A majority of the unchanged drug is excreted in the urine within 24 hours of ingestion. Up to 15% is excreted in the urine as an aldehyde and a dicarboxylic acid metabolite. Ethambutol doses may have to be modified in patients with renal failure.

Ethambutol has replaced aminosalicylic acid as a first-line antitubercular drug. It is commonly included as a fourth drug, along with isoniazid, pyrazinamide, and rifampin, in patients infected with MDR strains. It also is used in combination in the treatment of *M. avium-intracellulare* infection in AIDS patients.

The major toxicity associated with ethambutol use is retrobulbar neuritis impairing visual acuity and red-green color discrimination; this side effect is dose related and reverses slowly once the drug is discontinued. Mild GI intolerance, allergic reaction, fever, dizziness, and mental confusion are also possible. Hyperuricemia is associated with ethambutol use due to a decreased renal excretion of urates; gouty arthritis may result.

Streptomycin

Streptomycin, an aminoglycoside antibiotic (see Chapter 46), was the first drug shown to reduce tuberculosis mortality. Streptomycin is bactericidal against *M. tuberculosis* in vitro but is inactive against intracellular organisms. Most *M. tuberculosis* strains and nontuberculosis species, such as *M. kansasii* and *M. avium-intracellulare*, are sensitive. Spontaneous resistance to streptomycin, seen in approximately 1 in 10⁶ tubercle bacilli, is related to a point mutation that involves the gene (*rpsL* or *rrs*) that encodes for ribosomal proteins and binding sites. About 80% of strains that are resistant to isoniazid and rifampin are also resistant to streptomycin.

Streptomycin is indicated as a fourth drug in combination with isoniazid, rifampin, and pyrazinamide in patients at high risk for drug resistance. It is also used in the treatment of streptomycin-susceptible MDR tuberculosis.

Ototoxicity and nephrotoxicity are the major concerns during administration of streptomycin and other aminoglycosides. The toxic effects are dose related and increase with age and underlying renal insufficiency. All aminoglycosides require dose adjustment in renal failure patients. Ototoxicity is severe when aminoglycosides are combined with other potentially ototoxic agents.

SECOND-LINE ANTITUBERCULOUS DRUGS

Para-aminosalicylic Acid

Para-aminosalicylic Acid (PAS), like the sulfonamides (see Chapter 44), is a structural analogue of *p*-aminobenzoic acid (PABA). It is a folate synthesis antagonist that interferes with the incorporation of PABA into folic acid. PAS is bacteriostatic, and in vitro, most strains of *M. tuberculosis* are sensitive to a concentra-

tion of 1 µg/mL. The antibacterial activity of PAS is highly specific for *M. tuberculosis*; it is not effective against other mycobacterium species.

PAS is readily absorbed from the GI tract and is widely distributed throughout body fluids except cerebrospinal fluid. It penetrates tissues and reaches high concentrations in the tuberculous cavities and caseous tissue. Peak plasma levels are reached within 1 to 2 hours of drug administration, and the drug has a half-life of about an hour. PAS is primarily metabolized by hepatic acetylation. When combined with isoniazid, PAS can function as an alternative substrate and block hepatic acetylation of isoniazid, thereby increasing free isoniazid levels. Both the acetylated and unaltered drug are rapidly excreted in the urine. The concentration of PAS in urine is high and may result in crystalluria.

Use of PAS has diminished over the years following the introduction of more effective drugs, such as rifampin and ethambutol. At present, therapy with PAS is limited to the treatment of MDR tuberculosis. Problems with primary resistance, poor compliance due to GI intolerance, and lupuslike reactions have further discouraged its use.

Ethionamide

Ethionamide (*Trecator*) is a derivative of isonicotinic acid and is chemically related to isoniazid. It is a secondary agent used in combination when primary agents are ineffective or contraindicated; it is a bacteriostatic antituberculosis agent. Its exact mechanism of action is unknown but is believed to involve inhibition of oxygen-dependent mycolic acid synthesis. It is thought that mutations in the region of the (*inhA*) gene that are involved in mycolic acid synthesis can cause both isoniazid and ethionamide resistance.

Ethionamide is well absorbed following oral administration. It is rapidly and widely distributed to all body tissues and fluids, including the cerebrospinal fluid. Metabolism of ethionamide is extensive, and several dihydropyridine metabolites are produced. Less than 1% of the drug is eliminated in the urine unchanged.

GI disturbances, including nausea, vomiting, and intense gastric irritation, are frequent. In addition, ethionamide may cause a wide range of neurological side effects, such as confusion, peripheral neuropathy, psychosis, and seizures. Neurological effects can be minimized by pyridoxine supplementation. Other rare side effects include gynecomastia, impotence, postural hypotension, and menorrhagia.

Cycloserine

Cycloserine is a broad-spectrum antibiotic produced by *Streptomyces orchidaceus*. It is structural analogue of D-alanine and acts through a competitive inhibition of the

D-alanine that is involved in bacterial cell wall synthesis. Cycloserine is inhibitory to *M. tuberculosis* and active against *Escherichia coli*, *S. aureus*, and *Enterococcus*, *Nocardia*, and *Chlamydia* spp. It is used in the treatment of MDR tuberculosis and is useful in renal tuberculosis, since most of the drug is excreted unchanged in the urine.

Cycloserine is readily absorbed orally and distributes throughout body fluids including the cerebrospinal fluid. The concentrations of cycloserine in tissues, body fluids, and the cerebrospinal fluid are approximately equal to the plasma level. Cycloserine is partially metabolized, and 60 to 80% is excreted unchanged by the kidney.

Neurological symptoms, which tend to appear in the first week of therapy, consist of dizziness, confusion, irritability, psychotic behavioral changes, and even suicidal ideation. Cycloserine is contraindicated in patients with underlying psychiatric and seizure disorders. Other side effects include occasional peripheral neuropathy and low magnesium levels.

Rifabutin

Rifabutin (*Mycobutin*), an antibiotic related to rifampin, shares its mechanism of action, that is, inhibition of RNA polymerase. Rifabutin has significant activity in vitro and in vivo against *M. avium-intracellular* complex (MAC) isolates from both HIV-infected and non-HIV-infected individuals. It has better activity against MAC organisms than rifampin. Rifabutin is active against *M. tuberculosis*, including some rifampin-resistant strains, such as *M. leprae* and *M. fortuitum*. It has a spectrum of activity against gram-positive and gram-negative organisms similar to that of rifampin. The molecular basis for resistance to rifabutin is shared by both rifampin and rifabutin; this explains the virtually complete cross-resistance that occurs between these drugs.

Rifabutin is well absorbed orally, and peak plasma concentrations are reached in 2 to 3 hours. Because of its lipophilicity, rifabutin achieves a 5- to 10-fold higher concentration in tissues than in plasma. The drug has a half-life range of 16 to 96 hours and is eliminated in urine and bile.

Rifabutin appears as effective as rifampin in the treatment of drug-susceptible tuberculosis and is used in the treatment of latent tuberculosis infection either alone or in combination with pyrazinamide. Clinical use of rifabutin has increased in recent years, especially in the treatment of HIV infection. It is a less potent inducer of cytochrome 450 enzymes pathways than rifampin and results in less drug interaction with the protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Rifabutin is therefore commonly substituted for rifampin in the treatment of tuberculosis in HIV-infected patients. Another important use of rifabutin in the HIV-infected population is prevention and treatment of disseminated MAC.

The adverse effects that most frequently result in discontinuation of rifabutin include GI intolerance, rash, and neutropenia. Rifabutin levels will be increased with concurrent administration of fluconazole and clarithromycin, resulting in anterior uveitis, polymyalgia syndrome, and a yellowish-tan discoloration of the skin (pseudojaundice). Other adverse reactions are similar to those of rifampin, such as hepatitis, red-orange discoloration of body fluids, and drug interactions due to effects on the hepatic P450 cytochrome enzyme system.

Rifapentine

Rifapentine is an analogue of rifampin that is active against *M. tuberculosis* and *M. avium*. Rifapentine's mechanism of action, cross-resistance, hepatic induction of P450 enzymes, drug interactions, and toxic profile are similar to those of rifampin. It has been used in the treatment of tuberculosis caused by rifampin-susceptible strains.

Capreomycin

Capreomycin (*Capastat*) is a polypeptide antibiotic derived from *Streptomyces capreolus*. It is bacteriostatic against most strains of *M. tuberculosis*, including the MDR strain. In addition, it is active against *M. kansasii*, *M. avium*, and in high concentrations, some gram-positive and gram-negative bacteria. Like other antitubercular drugs, resistance to capreomycin occurs rapidly if the drug is used alone. There is no cross-resistance between streptomycin and capreomycin, but some isolates resistant to capreomycin are resistant to viomycin.

Capreomycin is poorly absorbed from GI tract and so must be given parenterally. It is excreted mainly unchanged in the urine following glomerular filtration. Capreomycin is used as a second-line agent in combination with other drugs. It appears to be particularly useful in multidrug regimens for the treatment of drug-resistant tuberculosis, especially with streptomycin resistance. Capreomycin is associated with ototoxicity and nephrotoxicity, and these adverse effects can be severe in patients with preexisting renal insufficiency.

Amikacin and Kanamycin

Amikacin and kanamycin (see Chapter 46) have been used in the treatment of tuberculosis. Amikacin is very active against several mycobacterium species; however, it is expensive and has significant toxicity. It is considered in the treatment of MDR tuberculosis after streptomycin and capreomycin. An additional use of amikacin is in the treatment of disseminated MAC in AIDS patients. There is no cross-resistance between streptomycin and other aminoglycosides; most *M. tuberculosis* strains that are resistant to streptomycin are

sensitive to kanamycin. The latter drug may be preferred over viomycin due to its lower toxicity.

Viomycin

Viomycin is a complex polypeptide antibiotic that is active against MDR strains of tuberculosis. Cross-resistance between viomycin and kanamycin is less frequent than between viomycin and capreomycin.

Clofazimine

Clofazimine has some activity against *M. tuberculosis* and is used as a last resort drug for the treatment of MDR tuberculosis. It is primarily used in the treatment of *M. leprae* and *M. avium-intracellulare*. Further details are discussed later, under the treatment of leprosy.

Macrolides

The macrolide antibiotics (see Chapter 47) clarithromycin and azithromycin have demonstrated in vitro activity against mycobacteria, although they have limited activity against *M. tuberculosis*. Clarithromycin is four times as active as azithromycin against *M. avium-intracellulare* in vitro. Azithromycin's lower potency may be compensated for by its greater intracellular penetration and its two-fold higher tissue levels than plasma levels. Clarithromycin with azithromycin, in combination with other drugs, has gained an important role in the prevention and treatment of MAC in HIV-infected patients.

Thiacetazone

Thiacetazone is active against many strains of *M. tuberculosis*. It is not marketed in the United States. However, because of its low cost, it is used as a first-line agent in East Africa, especially in combination with compounds such as isoniazid. The most common side effects of thiacetazone include GI intolerance and development of rashes. It causes significant ototoxicity, especially when coadministered with streptomycin. *Life-threatening hypersensitivity reactions, such as hepatitis, transient marrow aplastic syndromes, neutropenia, and thrombocytopenia, have been reported.*

Quinolones: Ciprofloxacin, Levofloxacin and Ofloxacin

Most of the fluoroquinolones antibiotics (see Chapter 44) have activity against *M. tuberculosis* and *M. avium-intracellulare*. Ciprofloxacin, ofloxacin, and levofloxacin inhibit 90% of the strains of susceptible tubercula bacilli at concentrations of less than 2 µg/mL. Levofloxacin is preferred because it is the active L-optical isomer of ofloxacin and is approved for once-daily use. The

quinolones act by inhibition of bacterial DNA gyrase. Resistance is the result of spontaneous mutations in genes that either change the DNA gyrase or decrease the ability of the drug to cross the cell membrane.

Quinolones are important recent additions to the therapeutic agents used against *M. tuberculosis*, especially in MDR strains. Clinical trials of ofloxacin in combination with isoniazid and rifampin have indicated activity comparable to that of ethambutol. In addition, quinolones, particularly ciprofloxacin, are used as part of a combined regimen in HIV-infected patients.

***β*-Lactam and Clavulanate Antibiotics**

All mycobacteria produce β -lactamase. In vitro, several β -lactamase-resistant antibiotics or a combination of a β -lactam with β -lactamase inhibitors, such as clavulanic acid, are active against *M. tuberculosis* and nontuberculous mycobacteria. However, the activity of β -lactam agents against intracellular mycobacteria is generally poor. The β -lactam agents may be useful in the treatment of MDR tuberculosis in combination with other antitubercular drugs but never as monotherapy.

RECOMMENDATION FOR THE TREATMENT OF LATENT TUBERCULOSIS INFECTION

Recently revised recommendations for the treatment of latent tuberculosis infection (LTBI) include new therapeutic regimens as follows:

Isoniazid for 9 months daily or twice weekly is preferred for all adults.

Or

Isoniazid for 6 months daily or twice weekly is acceptable for HIV-negative patients and is cost effective.

Or

Rifampin and pyrazinamide daily for 2 months is appropriate for isoniazid-resistant tuberculosis.

Or

Rifampin daily for 4 months may be given to individuals who cannot tolerate pyrazinamide.

RECOMMENDATIONS FOR TREATMENT OF ACTIVE TUBERCULOSIS

The most commonly used regimen for drug-susceptible tuberculosis consists of isoniazid, rifampin, and pyrazinamide daily for 2 months, followed by isoniazid and rifampin daily or two to three times a week for 4 months. If isoniazid resistance is suspected, ethambutol or streptomycin should be added to the regimen until the susceptibility of the mycobacterium is determined. This

regimen will provide at least two drugs to which the *M. tuberculosis* isolate is susceptible in more than 95% of patients in the United States.

Alternative regimens include isoniazid, rifampin, pyrazinamide, and either streptomycin or ethambutol for 2 weeks followed biweekly with the same regimen for 6 weeks, and subsequently with biweekly administration of isoniazid and rifampin for 16 weeks. In HIV-infected patients the treatment should be prolonged 9 to 12 months or sometimes even longer if the response is slow. Treatment of tuberculosis is more challenging in an HIV-infected population taking highly active antiretroviral therapy because of drug interactions.

TREATMENT OF LEPROSY

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. Host defenses are crucial in determining the patient's response to the disease, the clinical presentation, and the bacillary load. These factors also influence the length of therapy and the risk of adverse reactions to medication. *M. leprae* cannot be grown on routine laboratory culture media, so drug sensitivity testing in vitro is not possible. Growth and drug susceptibility testing are done by injecting into animal models.

One description of a clinical picture that results from *tuberculoid leprosy* is characterized by intact cell-mediated immunity, a positive lepromin skin reaction, granuloma formation, and a relative paucity of bacilli. At the other extreme, *lepromatous leprosy* is characterized by depressed cell-mediated immunity, numerous bacilli within the tissues, no granulomas, and a negative skin test for lepromin. Within these two extremes are the patients with an intermediate or borderline form of leprosy who show a variable lepromin reaction and few bacilli; they may progress to either tuberculoid or lepromatous leprosy.

Current recommendations for the treatment of leprosy suggest multidrug regimens rather than monotherapy because such a regimen has proven to be more effective, delays the emergence of resistance, prevents relapse, and shortens the duration of therapy. Established agents used in the treatment of leprosy are dapsone, clofazimine, and rifampin. Treatment of tuberculoid leprosy is continued for at least 1 to 2 years, while patients with lepromatous leprosy are generally treated for 5 years. In addition to chemotherapy, patients with leprosy need psychosocial support, rehabilitation, and surgical repair of any disfigurement.

Dapsone and Sulfones

The sulfones are structural analogues of PABA and are competitive inhibitors of folic acid synthesis. Sulfones are bacteriostatic and are used only in the treatment of

leprosy. Dapsone (*Avlosulfon*) is the most widely used sulfone for the long-term therapy of leprosy. Although the sulfones are highly effective against most strains of *M. leprae*, a small number of organisms, especially those found in lepromatous leprosy patients, are less susceptible and can persist for many years, resulting in relapse. Before the introduction of current multidrug regimens, resistance rates were as high as 20% with dapsone monotherapy.

Sulfones, such as dapsone and sulfoxone (*Diasone*), are well absorbed orally and are widely distributed throughout body fluids and tissues. Peak concentrations of dapsone are reached within 1 to 3 hours of oral administration and have a half-life of 21 to 44 hours; about 50% of administered dapsone is bound to serum proteins. The sulfones tend to remain in the skin, muscle, kidney, and liver up to 3 weeks after therapy is stopped. The concentration in inflamed skin is 10 to 15 times higher than that found in normal skin. The sulfones are retained in the circulation for a long time (12–35 days) because of hepatobiliary drug recirculation. The sulfones are acetylated in the liver, and 70 to 80% of drug is excreted in the urine as metabolites.

Dapsone, combined with other antileprosy agents like rifampin and clofazimine, is used in the treatment of both multibacillary and paucibacillary *M. leprae* infections. Dapsone is also used in the treatment and prevention of *Pneumocystis carinii* pneumonia in AIDS patients who are allergic to or intolerant of trimethoprim-sulfamethoxazole.

Acedapsone is a derivative of dapsone that has little activity against *M. leprae* but is converted to an active dapsone metabolite. It is a long-acting intramuscular repository form of dapsone with a half-life of 46 days. It may prove useful in leprosy patients who cannot tolerate long-term oral dapsone therapy.

The sulfones can produce nonhemolytic anemia, methemoglobinemia, and sometimes acute hemolytic anemia in persons with a glucose-6-phosphate dehydrogenase deficiency. Within a few weeks of therapy some

patients may develop acute skin lesions described as sulfone syndrome or dapsone dermatitis. Some rare side effects include fever, pruritus, paresthesia, reversible neuropathy, and hepatotoxicity.

Clofazimine

Clofazimine is a weakly bactericidal dye that has some activity against *M. leprae*. Its precise mechanism of action is unknown but may involve mycobacterial DNA binding. Its oral absorption is quite variable, with 9 to 70% of the drug eliminated in the feces. Clofazimine achieves significant concentrations in tissues, including the phagocytic cells; it has a plasma half-life of 70 days. It is primarily excreted in bile, with less than 1% excretion in urine.

Clofazimine is given to treat sulfone-resistant leprosy or to patients who are intolerant to sulfones. It also exerts an antiinflammatory effect and prevents erythema nodosum leprosum, which can interrupt treatment with dapsone. This is a major advantage of clofazimine over other antileprosy drugs. Ulcerative lesions caused by *Mycobacterium ulcerans* respond well to clofazimine. It also has some activity against *M. tuberculosis* and can be used as last resort therapy for the treatment of MDR tuberculosis.

The most disturbing adverse reaction to clofazimine is a red-brown discoloration of the skin, especially in light-skinned persons. A rare but serious adverse reaction is acute abdominal pain significant enough to warrant exploratory laparotomy or laparoscopy. Other infrequent side effects include splenic infarction, bowel obstruction, paralytic ileus, and upper GI bleeding.

Ethionamide and Prothionamide

Ethionamide and prothionamide are weakly bactericidal against *M. leprae* and can be used as alternatives to clofazimine in the treatment of MDR leprosy. Both cause GI intolerance and are expensive.

Study QUESTIONS

1. A 35-year-old man under treatment for pulmonary tuberculosis has acute-onset right big toe pain, swelling, and low-grade fever. His physical examination was consistent with gouty arthritis, and he was found to have high serum uric acid levels. Which of the following antituberculosis drugs is known to cause high uric acid levels?
 - (A) Cycloserine
 - (B) Thiacetazone
 - (C) Pyrazinamide
 - (D) Rifampin
 - (E) Aminosalicic acid
2. A 26-year-old truck driver, a recent immigrant from Mexico, could not obtain a Florida driving license because of his poor performance in red-green color vision discrimination. He denies any family history of color vision-related problems in the past. He is taking a four-drug regimen for pulmonary tubercu-

losis. He does not recall the names of the drugs.

Which of the following antituberculosis drugs is responsible for his lack of color vision discrimination?

- (A) Ethambutol
 - (B) Ethionamide
 - (C) Aminosalicic acid
 - (D) Rifampin
 - (E) Isoniazid
3. A 68-year-old white South African man receiving treatment for lepromatous leprosy has increasing red-brown pigmentation. Which of the following antileprosy drugs is responsible for the patient's skin pigmentation?
- (A) Dapsone
 - (B) Rifampin
 - (C) Clofazimine
 - (D) Capreomycin
 - (E) Thiacetazone
4. A 23 year-old college student is diagnosed with *Neisseria meningitidis* based on his clinical presentation, gram-negative diplococci on Gram stain, and isolation of bacteria from cerebrospinal fluid. Which of the following drugs can be used as a prophylactic agent for roommates and other close contacts?
- (A) Amoxicillin
 - (B) Isoniazid
 - (C) Dapsone
 - (D) Clarithromycin
 - (E) Rifampin
5. A 32-year-old Haitian man has acute-onset confusion and suicidal ideation. Two weeks ago he began combination therapy for multi-drug resistant pulmonary tuberculosis. He has a history of depression that required intermittent treatment in the past. Which of the following antitubercular agents is responsible for the patient's neurological symptoms?
- (A) Pyrazinamide
 - (B) Aminosalicic acid
 - (C) Cycloserine
 - (D) Rifampin
 - (E) Ethambutol

ANSWERS

1. **C.** Pyrazinamide is known to cause hyperuricemia and precipitate gouty arthritis. Pyrazinamide-induced gouty arthritis does not respond to uricosuric therapy with probenecid but may respond to acetylsalicic acid. Cycloserine (A) can cause headaches, confusion, tremors, and seizures, possibly secondary to low levels of magnesium in the cerebrospinal fluid; cycloserine should be avoided in patients with epilepsy and mental depression. It is not associated with hyperuricemia. Thiacetazone (B) is an antibiotic that is rarely used in tuberculosis. The most common adverse reactions are general rashes and GI intolerance. Its use is not associated with hy-

peruricemia. Rifampin (D) is associated with hepatitis, GI intolerance, drug interactions and a red-orange discoloration of saliva, tears, and urine. It is not associated with hyperuricemia. Aminosalicic acid (E) is sometimes associated with sodium overload and fluid retention when large doses of the sodium salt of PAS is administered; it is not associated with hyperuricemia.

2. **A.** Ethambutol is associated with retrobulbar neuritis, resulting in loss of central vision and impaired red-green discrimination. Ethionamide (B) is an analogue of isonicotinic acid and is associated with GI intolerance and peripheral neuropathy, but not the optic neuritis or color vision discrimination problems. Aminosalicic acid (C) can cause GI irritation and bleeding problems, so caution is required in peptic ulcer patients. It has no neurological side effects. Rifampin (D) is associated with red-orange discoloration of saliva, tears, and urine but not the color vision problems. Isoniazid (E) is associated with peripheral neuritis in chronic alcoholics and malnourished individuals and requires pyridoxine supplements. It is not associated with optic neuritis.
3. **C.** Clofazimine has antilepromatous and antiinflammatory properties. Its most disturbing side effect is red-brown pigmentation of skin, particularly in light-skinned persons. Dapsone (A) can produce rashes and erythema nodosum, including Stevens-Johnson syndrome (dapsone dermatitis), but it is not associated with altered skin pigmentation. Rifampin (B) imparts a harmless red-orange discoloration of saliva, sweat, urine, feces, tears, and contact lenses but is not associated with skin pigmentation changes. Capreomycin (D) is similar to streptomycin and can cause ototoxicity and nephrotoxicity. Its use is not associated with skin discoloration or pigment problems. Thiacetazone (E) is rarely used in the treatment of leprosy. Rashes and GI intolerance are common side effects. It is not associated with any skin discoloration or pigment problem.
4. **E.** Rifampin, commonly used in the prophylaxis of *Neisseriae meningitidis*, is given to individuals who are in close contact with someone having the disease. Other drugs that can be used include ciprofloxacin and sulfonamides. Amoxicillin (A) is used as prophylaxis of endocarditis in patients with a history of endocarditis or a preexisting valvular heart disease. Isoniazid (B) is a commonly used drug for latent tuberculosis infection in high-risk patients who are positive PPD and have a negative chest radiograph. Dapsone (C) is used as a chemoprophylactic agent for *Pneumocystis carinii* pneumonia in AIDS patients who are allergic or intolerant to trimethoprim-sulfamethoxazole. Clarithromycin (D) is used

as a chemoprophylactic agent for MAC in AIDS patients.

5. C. Cycloserine is associated with confusion, psychosis, and suicidal ideation; symptoms are usually seen within a week of therapy. Cycloserine should be avoided in patients with psychiatric disorders. Pyrazinamide (A) is associated with a hepatic dysfunction that must be closely monitored. Nearly all patients taking pyrazinamide develop hyperuricemia. It has no neurological side effects. Aminosalicyclic acid (B) is associated with GI intolerance, especially acute bleeding, due to severe gastritis. It has no neurological side effects. Rifampin (D) is associated with hepatitis, drug interactions, red-orange discoloration of body fluids, and rarely, a flulike syndrome. It has no neurological side effects. Ethambutol (E) is associated with retrobulbar neuritis and color vision impairment. It may cause peripheral neuritis but is not associated with behavioral problems.

SUPPLEMENTAL READING

- Small PM and Fujiwara PI. Medical progress: Management of tuberculosis in the United States. *N Engl J Med* 2001;345:189–200.
- Targeted tuberculin testing and treatment of latent infection. Centers For Disease Control and Prevention *MMWR* 2000;49:1–54.
- Updated Guidelines for the Use of Rifabutin or Rifampin for the Treatment and Prevention of Tuberculosis Among HIV-infected Patients Taking Protease Inhibitors or Non-nucleoside Reverse Transcriptase Inhibitors. Centers For Disease Control and Prevention *MMWR* 2000;49:185.
- Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection. *MMWR* 2001;50:733–735.
- WHO Expert Committee on Leprosy. *World Health Organ Tech Rep Ser* 1998;874:1–43.

CASE Study Genetic Influences on Metabolism

A 36-year-old steroid-dependent man, an asthmatic and injection drug user, presents with a cough, 10-lb weight loss, and general weakness. His recent HIV screening was negative. He is taking oral prednisone 20 mg per day and denies any drug allergies. Upon examination, he appears to be chronically ill with a low-grade temperature of 100°F (38°C). His physical examination produced benign findings except for bilateral rhonchi over the apical lung fields. A presumptive diagnosis of pulmonary tuberculosis is based on the history and the appearance of right apical infiltrates on the chest radiograph. Four-drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol was ordered along with pyridoxine supplements pending the final culture and susceptibilities.

Metabolism of which ONE of the above-mentioned drugs is genetically predetermined?

- (A) Rifampin
- (B) Isoniazid (INH)
- (C) Pyrazinamide
- (D) Ethambutol

ANSWER: B. Rifampin (A) is known to induce certain cytochrome P-450 enzymes and accelerates the metabolism of coadministered drugs that undergo biotransformation through CYP-450. No genetic predetermination is involved in this process. Isoniazid (B) is acetylated to acetyl isoniazid by *N*-acetyltransferase present in the liver. The human population shows heterogeneity with regard to the rate of acetylation. Rapid acetylators have higher ratios of acetyl isoniazid to isoniazid than do slow acetylators. This genetic determination is rarely important clinically. Pyrazinamide (C) is deaminated by the microsomal drug metabolizing enzyme pyrazinamide deaminase to form pyrazinoic acid. There is no genetic predetermination for this process. Ethambutol (D) is a synthetic antitubercular agent. Orally it is well absorbed and distributed, and about 15% is excreted in the form of two metabolites. This process is not genetically predetermined.