CHAPTER

46

Sulfonamides, Trimethoprim, & Quinolones

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CASE STUDY

A 59-year-old woman presents to an urgent care clinic with a 4-day history of frequent and painful urination. She has had fevers, chills, and flank pain for the past 2 days. Her physician advised her to come immediately to the clinic for evaluation. In the clinic she is febrile (38.5°C [101.3°F]) but otherwise stable and states she is not experiencing any nausea or vomiting. Her urine dipstick test is positive for leukocyte esterase. Urinalysis and urine culture are ordered. Her past medical history is significant for three urinary tract infections in the past year. Each episode was uncomplicated, treated with trimethoprim-sulfamethoxazole, and promptly resolved. She also has osteoporosis for which she takes a daily calcium supplement. The decision is made to treat her with oral antibiotics for a complicated urinary tract infection with close follow-up. Given her history, what would be a reasonable empiric antibiotic choice? Depending on the antibiotic choice are there potential drug interactions?

ANTIFOLATE DRUGS

SULFONAMIDES

Chemistry

The basic formulas of the sulfonamides and their structural similarity to *p*-aminobenzoic acid (PABA) are shown in Figure 46–1. Sulfonamides with varying physical, chemical, pharmacologic, and antibacterial properties are produced by attaching substituents to the amido group ($–SO_2–NH–R$) or the amino group ($–NH_2$) of the sulfanilamide nucleus. Sulfonamides tend to be much more soluble at alkaline than at acid pH. Most can be prepared as sodium salts, which are used for intravenous administration.

Mechanism of Action & Antimicrobial Activity

Sulfonamide-susceptible organisms, unlike mammals, cannot use exogenous folate but must synthesize it from PABA. This pathway (Figure 46–2) is thus essential for production of purines and nucleic acid synthesis. As structural analogs of PABA, sulfonamides inhibit dihydropteroate synthase and folate production. Sulfonamides inhibit both gram-positive and gram-negative bacteria, *Nocardia* sp, *Chlamydia trachomatis,* and some protozoa. Some enteric bacteria, such as *Escherichia coli, Klebsiella pneumoniae, Salmonella*, *Shigella*, and *Enterobacter* sp are also inhibited. It is interesting that rickettsiae are not inhibited by sulfonamides but are instead stimulated in their growth. Activity is poor against anaerobes. *Pseudomonas aeruginosa* is intrinsically resistant to sulfonamide antibiotics.

Combination of a sulfonamide with an inhibitor of dihydrofolate reductase (trimethoprim or pyrimethamine) provides synergistic activity because of sequential inhibition of folate synthesis (Figure 46–2).

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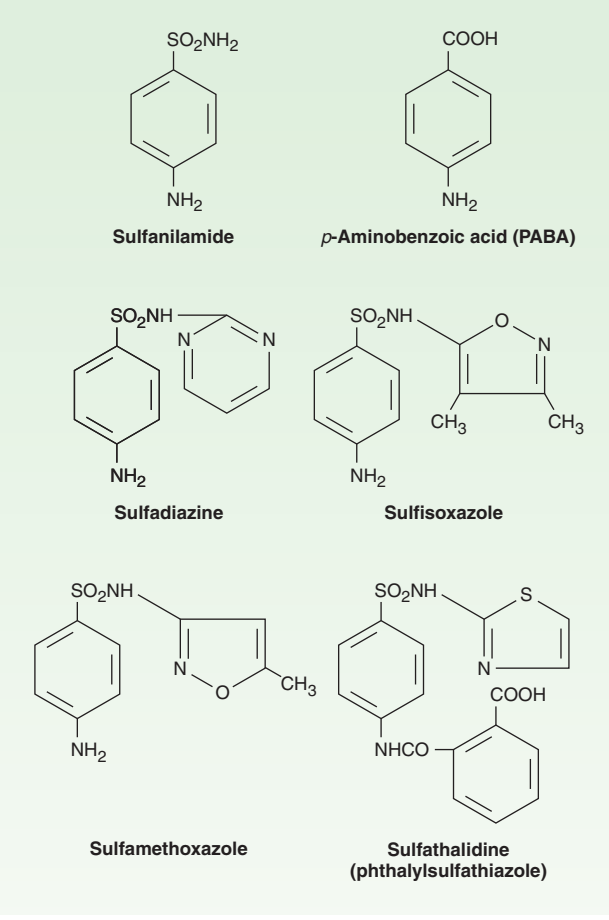


FIGURE 46–1 Structures of some sulfonamides and *p*-aminobenzoic acid.

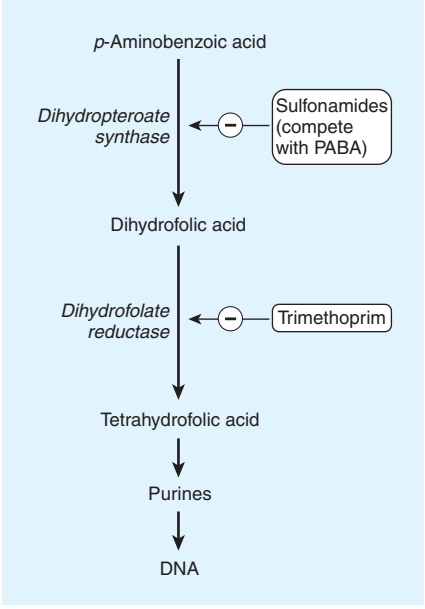


FIGURE 46–2 Actions of sulfonamides and trimethoprim.

Resistance

Mammalian cells (and some bacteria) lack the enzymes required for folate synthesis from PABA and depend on exogenous sources of folate; therefore, they are not susceptible to sulfonamides. Sulfonamide resistance may occur as a result of mutations that (1) cause overproduction of PABA, (2) cause production of a folic acid-synthesizing enzyme that has low affinity for sulfonamides, or (3) impair permeability to the sulfonamide. Dihydropteroate synthase with low sulfonamide affinity is often encoded on a plasmid that is transmissible and can disseminate rapidly and widely. Sulfonamide-resistant dihydropteroate synthase mutants also can emerge under selective pressure.

Pharmacokinetics

Sulfonamides can be divided into three major groups: (1) oral, absorbable; (2) oral, nonabsorbable; and (3) topical. The oral, absorbable sulfonamides can be classified as short-, intermediate-, or long-acting on the basis of their half-lives (Table 46–1). They are absorbed from the stomach and small intestine and distributed widely to tissues and body fluids (including the central nervous system and cerebrospinal fluid), placenta, and fetus. Protein binding varies from 20% to over 90%. Therapeutic concentrations are in the range of 40–100 mcg/mL of blood. Blood levels generally peak 2–6 hours after oral administration.

A portion of absorbed drug is acetylated or glucuronidated in the liver. Sulfonamides and inactive metabolites are then excreted into the urine, mainly by glomerular filtration. In significant renal failure, the dosage of sulfonamide must be reduced.

TABLE 46–1 Pharmacokinetic properties of some sulfonamides and pyrimidines.

Drug	Half-Life	Oral Absorption
Sulfonamides		
Sulfacytine	Short	Prompt (peak levels in 1–4 hours)
Sulfisoxazole	Short (6 hours)	Prompt
Sulfamethizole	Short (9 hours)	Prompt
Sulfadiazine	Intermediate (10–17 hours)	Slow (peak levels in 4–8 hours)
Sulfamethoxazole	Intermediate (10–12 hours)	Slow
Sulfapyridine	Intermediate (17 hours)	Slow
Sulfadoxine	Long (7–9 days)	Intermediate
Pyrimidines		
Trimethoprim	Intermediate (11 hours)	Prompt
Pyrimethamine	Long (4–6 days)	Prompt

Clinical Uses

Sulfonamides are infrequently used as single agents. Many strains of formerly susceptible species, including meningococci, pneumococci, streptococci, staphylococci, and gonococci, are now resistant. The fixed-drug combination of trimethoprim-sulfamethoxazole is the drug of choice for infections such as *Pneumocystis jiroveci* (formerly *P carinii*) pneumonia, toxoplasmosis, nocardiosis, and occasionally other bacterial infections.

A. Oral Absorbable Agents

Sulfisoxazole and sulfamethoxazole are short- to medium-acting agents used almost exclusively to treat urinary tract infections. The usual adult dosage is 1 g of sulfisoxazole four times daily or 1 g of sulfamethoxazole two or three times daily.

Sulfadiazine in combination with pyrimethamine is first-line therapy for treatment of acute toxoplasmosis. The combination of sulfadiazine with pyrimethamine, a potent inhibitor of dihydrofolate reductase, is synergistic because these drugs block sequential steps in the folate synthetic pathway blockade (Figure 46–2). The dosage of sulfadiazine is 1 g four times daily, with pyrimethamine given as a 75-mg loading dose followed by a 25-mg once-daily dose. Folinic acid, 10 mg orally each day, should also be administered to minimize bone marrow suppression.

Sulfadoxine is the only long-acting sulfonamide currently available in the USA and only as a combination formulation with pyrimethamine (Fansidar), a second-line agent in the treatment of malaria (see Chapter 52).

B. Oral Nonabsorbable Agents

Sulfasalazine (salicylazosulfapyridine) is widely used in ulcerative colitis, enteritis, and other inflammatory bowel disease (see Chapter 62).

C. Topical Agents

Sodium sulfacetamide ophthalmic solution or ointment is effective in the treatment of bacterial conjunctivitis and as adjunctive therapy for trachoma. Another sulfonamide, mafenide acetate, is used topically but can be absorbed from burn sites. The drug and its primary metabolite inhibit carbonic anhydrase and can cause metabolic acidosis, a side effect that limits its usefulness. Silver sulfadiazine is a much less toxic topical sulfonamide and is preferred to mafenide for prevention of infection of burn wounds.

Adverse Reactions

All sulfonamides, including antimicrobial sulfas, diuretics, diazoxide, and the sulfonylurea hypoglycemic agents, have been considered to be partially cross-allergenic. However, evidence for this is not extensive. The most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, diarrhea, and difficulties referable to the urinary tract (see below). Stevens-Johnson syndrome, although relatively uncommon (< 1% of treatment courses), is a particularly serious and potentially fatal type of skin and mucous membrane eruption associated with sulfonamide use. Other unwanted effects include stomatitis, conjunctivitis, arthritis, hematopoietic disturbances (see below), hepatitis, and, rarely, polyarteritis nodosa and psychosis.

A. Urinary Tract Disturbances

Sulfonamides may precipitate in urine, especially at neutral or acid pH, producing crystalluria, hematuria, or even obstruction. This is rarely a problem with the more soluble sulfonamides (eg, sulfisoxazole). Sulfadiazine when given in large doses, particularly if fluid intake is poor, can cause crystalluria. Crystalluria is treated by administration of sodium bicarbonate to alkalinize the urine and fluids to increase urine flow. Sulfonamides have also been implicated in various types of nephrosis and in allergic nephritis.

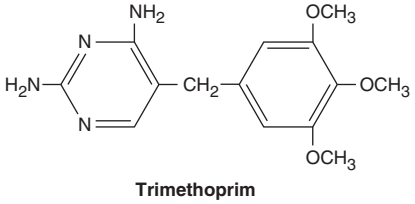
B. Hematopoietic Disturbances

Sulfonamides can cause hemolytic or aplastic anemia, granulocytopenia, thrombocytopenia, or leukemoid reactions. Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency. Sulfonamides taken near the end of pregnancy increase the risk of kernicterus in newborns.

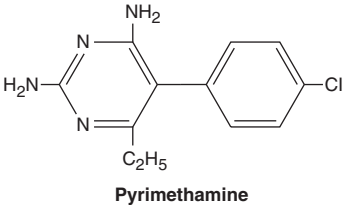
TRIMETHOPRIM & TRIMETHOPRIM-SULFAMETHOXAZOLE MIXTURES

Mechanism of Action

Trimethoprim, a trimethoxybenzylpyrimidine, selectively inhibits bacterial dihydrofolic acid reductase, which converts dihydrofolic acid to tetrahydrofolic acid, a step leading to the synthesis of purines and ultimately to DNA (Figure 46–2). Trimethoprim is about 50,000 times less efficient in inhibition of mammalian dihydrofolic acid reductase. Pyrimethamine, another benzylpyrimidine, selectively inhibits dihydrofolic acid reductase of protozoa compared with that of mammalian cells. As noted above, trimethoprim or pyrimethamine in combination with a sulfonamide blocks sequential steps in folate synthesis, resulting in marked enhancement (synergism) of the activity of both drugs. The combination often is bactericidal, compared with the bacteriostatic activity of a sulfonamide alone.



Trimethoprim



Pyrimethamine

Resistance

Resistance to trimethoprim can result from reduced cell permeability, overproduction of dihydrofolate reductase, or production of an altered reductase with reduced drug binding. Resistance can emerge by mutation, although more commonly it is due to plasmid-encoded trimethoprim-resistant dihydrofolate reductases. These resistant enzymes may be coded within transposons on conjugative plasmids that exhibit a broad host range, accounting for rapid and widespread dissemination of trimethoprim resistance among numerous bacterial species.

Pharmacokinetics

Trimethoprim is usually given orally, alone or in combination with sulfamethoxazole, which has a similar half-life. Trimethoprim-sulfamethoxazole can also be given intravenously. Trimethoprim is well absorbed from the gut and distributed widely in body fluids and tissues, including cerebrospinal fluid.

Because trimethoprim is more lipid-soluble than sulfamethoxazole, it has a larger volume of distribution than the latter drug. Therefore, when 1 part of trimethoprim is given with 5 parts of sulfamethoxazole (the ratio in the formulation), the peak plasma concentrations are in the ratio of 1:20, which is optimal for the combined effects of these drugs in vitro. About 30–50% of the sulfonamide and 50–60% of the trimethoprim (or their respective metabolites) are excreted in the urine within 24 hours. The dose should be reduced by half for patients with creatinine clearances of 15–30 mL/min.

Trimethoprim (a weak base) concentrates in prostatic fluid and in vaginal fluid, which are more acidic than plasma. Therefore, it has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.

Clinical Uses

A. Oral Trimethoprim

Trimethoprim can be given alone (100 mg twice daily) in acute urinary tract infections. Many community-acquired organisms are susceptible to the high concentrations that are found in the urine (200–600 mcg/mL).

B. Oral Trimethoprim-Sulfamethoxazole (TMP-SMZ)

A combination of trimethoprim-sulfamethoxazole is effective treatment for a wide variety of infections including *P jiroveci* pneumonia, shigellosis, systemic salmonella infections, urinary tract infections, prostatitis, and some nontuberculous mycobacterial infections. It is active against most *Staphylococcus aureus* strains, both methicillin-susceptible and methicillin-resistant, and against respiratory tract pathogens such as pneumococcus, *Haemophilus* sp, *Moraxella catarrhalis,* and *K pneumoniae* (but not *Mycoplasma pneumoniae*). However, the increasing prevalence of strains of *E coli* (up to 30% or more) and pneumococci that are resistant to trimethoprim-sulfamethoxazole must be considered before using this combination for empiric therapy of upper urinary tract infections or pneumonia.

One double-strength tablet (each tablet contains trimethoprim 160 mg plus sulfamethoxazole 800 mg) given every 12 hours is effective treatment for urinary tract infections and prostatitis. One half of the regular (single-strength) tablet given three times weekly for many months may serve as prophylaxis in recurrent urinary tract infections of some women. One double-strength tablet every 12 hours is effective treatment for infections caused by susceptible strains of shigella and salmonella. The dosage for children treated for shigellosis, urinary tract infection, or otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole every 12 hours.

Infections with *P jiroveci* and some other pathogens can be treated orally with high doses of the combination (dosed on the basis of the trimethoprim component at 15–20 mg/kg/d) or can be prevented in immunosuppressed patients by one double-strength tablet daily or three times weekly.

C. Intravenous Trimethoprim-Sulfamethoxazole

A solution of the mixture containing 80 mg trimethoprim plus 400 mg sulfamethoxazole per 5 mL diluted in 125 mL of 5% dextrose in water can be administered by intravenous infusion over 60–90 minutes. It is the agent of choice for moderately severe to severe pneumocystis pneumonia. It may be used for gram-negative bacterial sepsis, including that caused by some multidrug-resistant species such as enterobacter and serratia; shigellosis; typhoid fever; or urinary tract infection caused by a susceptible organism when the patient is unable to take the drug by mouth. The dosage is 10–20 mg/kg/d of the trimethoprim component.

D. Oral Pyrimethamine with Sulfonamide

Pyrimethamine and sulfadiazine have been used for treatment of leishmaniasis and toxoplasmosis. In falciparum malaria, the combination of pyrimethamine with sulfadoxine (Fansidar) has been used (see Chapter 52).

Adverse Effects

Trimethoprim produces the predictable adverse effects of an antifolate drug, especially megaloblastic anemia, leukopenia, and granulocytopenia. The combination trimethoprim-sulfamethoxazole may cause all of the untoward reactions associated with sulfonamides. Nausea and vomiting, drug fever, vasculitis, renal damage, and central nervous system disturbances occasionally occur also. Patients with AIDS and pneumocystis pneumonia have a particularly high frequency of untoward reactions to trimethoprim-sulfamethoxazole, especially fever, rashes, leukopenia, diarrhea, elevations of hepatic aminotransferases, hyperkalemia, and hyponatremia.

■ DNA GYRASE INHIBITORS

FLUOROQUINOLONES

The important quinolones are synthetic fluorinated analogs of nalidixic acid (Figure 46–3). They are active against a variety of gram-positive and gram-negative bacteria.

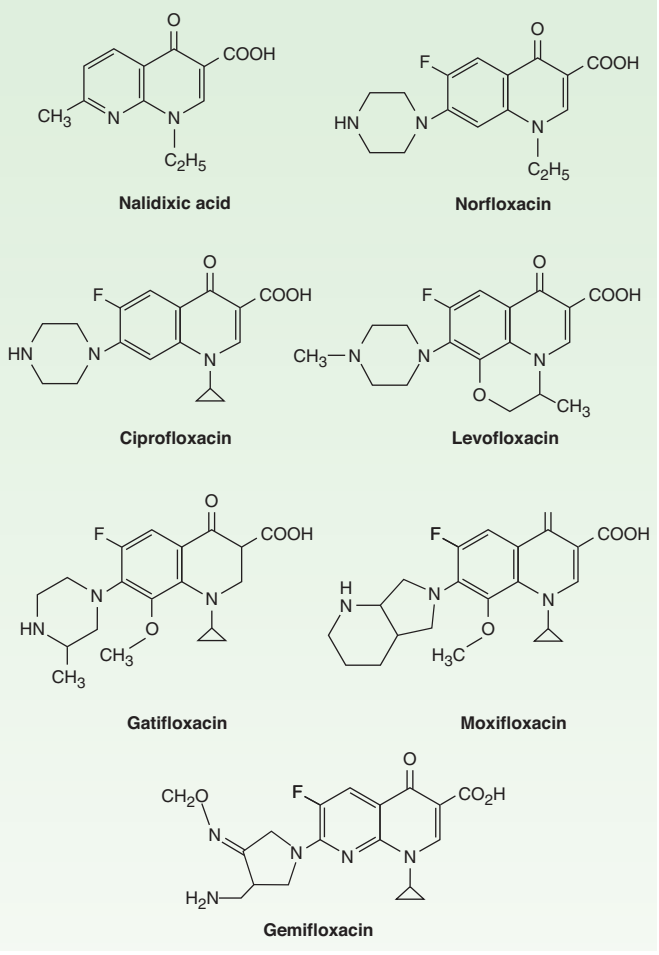


FIGURE 46–3 Structures of nalidixic acid and some fluoroquinolones.

Mechanism of Action

Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication. Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

Antibacterial Activity

Earlier quinolones such as nalidixic acid did not achieve systemic antibacterial levels and were useful only in the treatment of lower urinary tract infections. Fluorinated derivatives (ciprofloxacin, levofloxacin, and others; Figure 46–3 and Table 46–2) have greatly improved antibacterial activity compared with nalidixic acid and achieve bactericidal levels in blood and tissues.

Fluoroquinolones were originally developed because of their excellent activity against gram-negative aerobic bacteria; they had limited activity against gram-positive organisms. Several newer agents have improved activity against gram-positive cocci. This relative activity against gram-negative versus gram-positive species is useful for classification of these agents. Norfloxacin is the least active of the fluoroquinolones against both gram-negative and gram-positive organisms, with minimum inhibitory concentrations (MICs) fourfold to eightfold higher than those of ciprofloxacin. Ciprofloxacin, enoxacin, lomefloxacin, levofloxacin, ofloxacin, and pefloxacin comprise a second group of similar agents possessing excellent gram-negative activity and moderate to good activity against gram-positive bacteria. MICs for gram-negative cocci and bacilli, including *Enterobacter* sp, *P aeruginosa*, *Neisseria meningitidis*, *Haemophilus* sp, and *Campylobacter jejuni*, are 1–2 mcg/mL and often less. Methicillin-susceptible strains of *S aureus* are generally susceptible to these fluoroquinolones, but methicillin-resistant strains of staphylococci are often resistant. Streptococci and enterococci tend to be less susceptible than staphylococci, and efficacy in infections caused by these organisms is limited. Ciprofloxacin is the most active agent of this group against gram-negative organisms, *P aeruginosa* in particular. Levofloxacin, the L-isomer of ofloxacin, has superior activity against gram-positive organisms, including *Streptococcus pneumoniae.*

Gatifloxacin, gemifloxacin, and moxifloxacin make up a third group of fluoroquinolones with improved activity against gram-positive organisms, particularly *S pneumoniae* and some staphylococci. Gemifloxacin is active in vitro against ciprofloxacin-resistant strains of *S pneumoniae,* but in vivo efficacy is unproven. Although MICs of these agents for staphylococci are lower than those of ciprofloxacin (and the other compounds mentioned in the paragraph above), it is not known whether the enhanced activity is sufficient to permit use of these agents for treatment of infections caused by ciprofloxacin-resistant strains. In general, none of these agents is as active as ciprofloxacin against gram-negative organisms. Fluoroquinolones also are active against agents of atypical pneumonia (eg, mycoplasmas and chlamydiae) and against intracellular pathogens such as *Legionella pneumophila* and some mycobacteria, including *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. Moxifloxacin also has modest activity against anaerobic bacteria. Because of toxicity, gatifloxacin is no longer available in the United States.

Resistance

During fluoroquinolone therapy, resistant organisms emerge in about one of every 10^7–10^9 organisms, especially among staphylococci, *P aeruginosa*, and *Serratia marcescens.* Resistance is due to one or more point mutations in the quinolone binding region of the target enzyme or to a change in the permeability of the organism. However, this does not account for the relative ease with which resistance develops in exquisitely susceptible bacteria. More recently two types of plasmid-mediated resistance have been described. The first type utilizes Qnr proteins, which protect DNA gyrase from the fluoroquinolones. The second is a variant of an aminoglycoside acetyltransferase capable of modifying ciprofloxacin. Both mechanisms confer low-level resistance that may facilitate the point mutations that confer high-level resistance. Resistance to one fluoroquinolone, particularly if it is of high level, generally confers cross-resistance to all other members of this class.

TABLE 46–2 Pharmacokinetic properties of some fluoroquinolones.

Drug	Half-Life (h)	Oral Bioavailability (%)	Peak Serum Concentration (mcg/mL)	Oral Dose (mg)	Primary Route of Excretion
Ciprofloxacin	3–5	70	2.4	500	Renal
Gatifloxacin	8	98	3.4	400	Renal
Gemifloxacin	8	70	1.6	320	Renal and nonrenal
Levofloxacin	5–7	95	5.7	500	Renal
Lomefloxacin	8	95	2.8	400	Renal
Moxifloxacin	9–10	> 85	3.1	400	Nonrenal
Norfloxacin	3.5–5	80	1.5	400	Renal
Ofloxacin	5–7	95	2.9	400	Renal

Pharmacokinetics

After oral administration, the fluoroquinolones are well absorbed (bioavailability of 80–95%) and distributed widely in body fluids and tissues (Table 46–2). Serum half-lives range from 3 to 10 hours. The relatively long half-lives of levofloxacin, gemifloxacin, gatifloxacin, and moxifloxacin permit once-daily dosing. Oral absorption is impaired by divalent and trivalent cations, including those in antacids. Therefore, oral fluoroquinolones should be taken 2 hours before or 4 hours after any products containing these cations. Serum concentrations of intravenously administered drug are similar to those of orally administered drug. Most fluoroquinolones are eliminated by renal mechanisms, either tubular secretion or glomerular filtration (Table 46–2). Dosage adjustment is required for patients with creatinine clearances less than 50 mL/min, the exact adjustment depending on the degree of renal impairment and the specific fluoroquinolone being used. Dosage adjustment for renal failure is not necessary for moxifloxacin. Nonrenally cleared fluoroquinolones are relatively contraindicated in patients with hepatic failure.

Clinical Uses

Fluoroquinolones (other than moxifloxacin, which achieves relatively low urinary levels) are effective in urinary tract infections caused by many organisms, including *P aeruginosa*. These agents are also effective for bacterial diarrhea caused by *Shigella*, *Salmonella*, toxigenic *E coli,* and *Campylobacter*. Fluoroquinolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been used in infections of soft tissues, bones, and joints and in intra-abdominal and respiratory tract infections, including those caused by multidrug-resistant organisms such as *Pseudomonas* and *Enterobacter*. Ciprofloxacin is a drug of choice for prophylaxis and treatment of anthrax, although the newer fluoroquinolones are active in vitro and very likely in vivo as well.

Ciprofloxacin and levofloxacin are no longer recommended for the treatment of gonococcal infection in the United States as resistance is now common. However, both drugs are effective in treating chlamydial urethritis or cervicitis. Ciprofloxacin, levofloxacin, or moxifloxacin is occasionally used for treatment of tuberculosis and atypical mycobacterial infections. These agents may be suitable for eradication of meningococci from carriers or for prophylaxis of infection in neutropenic cancer patients.

With their enhanced gram-positive activity and activity against atypical pneumonia agents (chlamydiae, *Mycoplasma*, and *Legionella*), levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin—so-called respiratory fluoroquinolones—are effective and used increasingly for treatment of upper and lower respiratory tract infections.

Adverse Effects

Fluoroquinolones are generally well tolerated. The most common effects are nausea, vomiting, and diarrhea. Occasionally, headache, dizziness, insomnia, skin rash, or abnormal liver function tests develop. Photosensitivity has been reported with lomefloxacin and pefloxacin. QT_c prolongation may occur with gatifloxacin, levofloxacin, gemifloxacin, and moxifloxacin, which should be avoided or used with caution in patients with known QT_c interval prolongation or uncorrected hypokalemia; in those receiving class IA (eg, quinidine or procainamide) or class III antiarrhythmic agents (sotalol, ibutilide, amiodarone); and in patients receiving other agents known to increase the QT_c interval (eg, erythromycin, tricyclic antidepressants). Gatifloxacin has been associated with hyperglycemia in diabetic patients and with hypoglycemia in patients also receiving oral hypoglycemic agents. Because of these serious effects (including some fatalities), gatifloxacin was withdrawn from sales in the United States in 2006; it may be available elsewhere.

Fluoroquinolones may damage growing cartilage and cause an arthropathy. Thus, these drugs are not routinely recommended for patients under 18 years of age. However, the arthropathy is reversible, and there is a growing consensus that fluoroquinolones may be used in children in some cases (eg, for treatment of pseudomonal infections in patients with cystic fibrosis). Tendonitis, a rare complication that has been reported in adults, is potentially more serious because of the risk of tendon rupture. Risk factors for tendonitis include advanced age, renal insufficiency, and concurrent steroid use. Fluoroquinolones should be avoided during pregnancy in the absence of specific data documenting their safety.

SUMMARY Sulfonamides, Trimethoprim, and Fluoroquinolones

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
FOLATE ANTAGONISTS				
• Trimethoprim-sulfamethoxazole	Synergistic combination of folate antagonists blocks purine production and nucleic acid synthesis	Bactericidal activity against susceptible bacteria	Urinary tract infections • *P jiroveci* pneumonia • toxoplasmosis • nocardiosis	Oral, IV • renal clearance (half-life 8 h) • dosed every 8–12 h • formulated in a 5:1 ratio of sulfamethoxazole to trimethoprim • *Toxicity:* Rash, fever, bone marrow suppression, hyperkalemia
• *Sulfisoxazole: Oral; used only for lower urinary tract infections*				
• *Sulfadiazine: Oral; first-line therapy for toxoplasmosis when combined with pyrimethamine*				
• *Trimethoprim: Oral; used only for lower urinary tract infections; may be safely prescribed to patients with sulfonamide allergy*				
• *Pyrimethamine: Oral; first-line therapy for toxoplasmosis when combined with sulfadiazine; coadminister with leucovorin to limit bone marrow toxicity*				
• *Pyrimethamine-sulfadoxine: Oral; second-line malaria treatment*				
FLUOROQUINOLONES				
• Ciprofloxacin	Inhibits DNA replication by binding to DNA gyrase and topoisomerase IV	Bactericidal activity against susceptible bacteria	Urinary tract infections • gastroenteritis • osteomyelitis • anthrax	Oral, IV • mixed clearance (half-life 4 h) • dosed every 12 h • divalent and trivalent cations impair oral absorption • *Toxicity:* Gastrointestinal upset, neurotoxicity, tendonitis
• *Ofloxacin: Oral; has improved pharmacokinetics and pharmacodynamics; use is limited to urinary tract infections and nongonococcal urethritis and cervicitis*				
• *Levofloxacin: Oral, IV; L-isomer of ofloxacin; once-daily dosing; renal clearance; "respiratory" fluoroquinolone with improved activity versus pneumococcus*				
• *Moxifloxacin: Oral, IV; "respiratory" fluoroquinolone; once-daily dosing; improved activity versus anaerobes and* M tuberculosis; *hepatic clearance results in lower urinary levels so use in urinary tract infections is not recommended*				
• *Gemifloxacin: Oral; "respiratory" fluoroquinolone*				

PREPARATIONS AVAILABLE

GENERAL-PURPOSE SULFONAMIDES

Sulfadiazine (generic)
Oral: 500 mg tablets

Sulfisoxazole (generic)
Oral: 500 mg tablets; 500 mg/5 mL syrup

SULFONAMIDES FOR SPECIAL APPLICATIONS

Mafenide (Sulfamylon)
Topical: 85 mg/g cream; 5% solution

Silver sulfadiazine (generic, Silvadene)
Topical: 10 mg/g cream

Sulfacetamide sodium (generic)
Ophthalmic: 1, 10, 15, 30% solutions; 10% ointment

TRIMETHOPRIM

Trimethoprim (generic, Proloprim, Trimpex)
Oral: 100, 200 mg tablets

Trimethoprim-sulfamethoxazole [co-trimoxazole, TMP-SMZ] (generic, Bactrim, Septra, others)
Oral: 80 mg trimethoprim + 400 mg sulfamethoxazole per single-strength tablet; 160 mg trimethoprim + 800 mg sulfamethoxazole per double-strength tablet; 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 mL suspension
Parenteral: 80 mg trimethoprim + 400 mg sulfamethoxazole per 5 mL for infusion (in 5 mL ampules and 5, 10, 20 mL vials)

PYRIMETHAMINE

Pyrimethamine (generic, Daraprim)
Oral: 25 mg tablets

Pyrimethamine-sulfadoxine (Fansidar)
Oral: 25 mg pyrimethamine + 500 mg sulfadoxine per tablet

QUINOLONES & FLUOROQUINOLONES

Ciprofloxacin (generic, Cipro, Cipro I.V.)
Oral: 100, 250, 500, 750 mg tablets; 500, 1000 mg extended-release tablet; 50, 100 mg/mL suspension
Parenteral: 10 mg/mL for IV infusion
Ophthalmic (Ciloxan): 3 mg/mL solution; 3.3 mg/g ointment

Gemifloxacin (Factive)
Oral: 320 mg tablet

Levofloxacin (Levaquin)
Oral: 250, 500, 750 mg tablets; 25 mg/mL solution
Parenteral: 5, 25 mg/mL for IV injection
Ophthalmic (Quixin): 5 mg/mL solution

Lomefloxacin (Maxaquin)
Oral: 400 mg tablets

Moxifloxacin (Avelox, Avelox I.V.)
Oral: 400 mg tablets
Parenteral: 400 mg in IV bag

Norfloxacin (Noroxin)
Oral: 400 mg tablets

Ofloxacin (Floxin)
Oral: 200, 300, 400 mg tablets
Ophthalmic (Ocuflox): 3 mg/mL solution
Otic (Floxin Otic): 0.3% solution

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CASE STUDY ANSWER

A fluoroquinolone that achieves good urinary levels (ciprofloxacin or levofloxacin) would be a reasonable choice for empiric treatment of this patient's complicated urinary tract infection. Her recent exposure to multiple courses of trimethoprim-sulfamethoxazole increases her chances of having a urinary tract infection with an isolate that is resistant to this antibiotic, making trimethoprim-sulfamethoxazole a poor choice. The patient should be told to take the oral fluoroquinolone 2 hours before or 4 hours after her calcium supplement as divalent and trivalent cations can significantly impair the absorption of oral fluoroquinolones.

CHAPTER 47

Antimycobacterial Drugs

Daniel H. Deck, PharmD, & Lisa G. Winston, MD*

CASE STUDY

A 45-year-old homeless man presents to the emergency department complaining of a 2-month history of fatigue, weight loss (10 kg), fevers, night sweats, and a productive cough. He is currently living on the street but has spent time in homeless shelters and prison in the last several years. He reports drinking 2–3 pints of hard alcohol per day for the last 15 years, and also reports a history of intravenous drug use. In the emergency department, a chest x-ray shows a right apical infiltrate. Given the high suspicion for pulmonary tuberculosis, the patient is placed in respiratory isolation. His first sputum smear shows many acid-fast bacilli, and a rapid HIV antibody test returns with a positive result. What drugs should be started for treatment of presumptive pulmonary tuberculosis? Does the patient have a heightened risk of developing medication toxicity? If so, which medication(s) would be likely to cause toxicity?

Mycobacteria are intrinsically resistant to most antibiotics. Because they grow more slowly than other bacteria, antibiotics that are most active against rapidly growing cells are relatively ineffective. Mycobacterial cells can also be dormant and thus completely resistant to many drugs or killed only very slowly. The lipid-rich mycobacterial cell wall is impermeable to many agents. Mycobacterial species are intracellular pathogens, and organisms residing within macrophages are inaccessible to drugs that penetrate these cells poorly. Finally, mycobacteria are notorious for their ability to develop resistance. Combinations of two or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy. The response of mycobacterial infections to chemotherapy is slow, and treatment must be administered for months to years, depending on which drugs are used. The drugs used to treat tuberculosis, atypical mycobacterial infections, and leprosy are described in this chapter.

*The authors thank Henry F. Chambers, MD, for his contributions to previous editions.

DRUGS USED IN TUBERCULOSIS

Isoniazid (INH), rifampin (or other rifamycin), pyrazinamide, ethambutol, and **streptomycin** are the five first-line agents for treatment of tuberculosis (Table 47–1). Isoniazid and rifampin are the most active drugs. An isoniazid-rifampin combination administered for 9 months will cure 95–98% of cases of tuberculosis caused by susceptible strains. The addition of pyrazinamide to an isoniazid-rifampin combination for the first 2 months allows the total duration of therapy to be reduced to 6 months without loss of efficacy (Table 47–2). In practice, therapy is initiated with a four-drug regimen of isoniazid, rifampin, and pyrazinamide plus either ethambutol or streptomycin until susceptibility of the clinical isolate has been determined. Neither ethambutol nor streptomycin adds substantially to the overall activity of the regimen (ie, the duration of treatment cannot be further reduced if either drug is used), but they provide additional coverage if the isolate proves to be resistant to isoniazid, rifampin, or both. The prevalence of isoniazid resistance among clinical isolates in the United States is approximately 10%. Prevalence of resistance to both isoniazid and rifampin (ie, multidrug resistance) is about 3%.

TABLE 47–1 Antimicrobials used in the treatment of tuberculosis.

Drug	Typical Adult Dosage[1]
First-line agents (in approximate order of preference)	
Isoniazid	300 mg/d
Rifampin	600 mg/d
Pyrazinamide	25 mg/kg/d
Ethambutol	15–25 mg/kg/d
Streptomycin	15 mg/kg/d
Second-line agents	
Amikacin	15 mg/kg/d
Aminosalicylic acid	8–12 g/d
Capreomycin	15 mg/kg/d
Ciprofloxacin	1500 mg/d, divided
Clofazimine	200 mg/d
Cycloserine	500–1000 mg/d, divided
Ethionamide	500–750 mg/d
Levofloxacin	500 mg/d
Rifabutin	300 mg/d[2]
Rifapentine	600 mg once or twice weekly

[1]Assuming normal renal function.

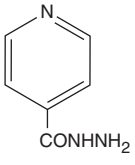
[2]150 mg/d if used concurrently with a protease inhibitor.

TABLE 47–2 Recommended duration of therapy for tuberculosis.

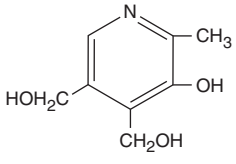
Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥ 24

ISONIAZID

Isoniazid is the most active drug for the treatment of tuberculosis caused by susceptible strains. It is a small molecule (MW 137) that is freely soluble in water. The structural similarity to pyridoxine is shown below.



Isoniazid



Pyridoxine

In vitro, isoniazid inhibits most tubercle bacilli at a concentration of 0.2 mcg/mL or less and is bactericidal for actively growing tubercle bacilli. It is less effective against atypical mycobacterial species. Isoniazid penetrates into macrophages and is active against both extracellular and intracellular organisms.

Mechanism of Action & Basis of Resistance

Isoniazid inhibits synthesis of mycolic acids, which are essential components of mycobacterial cell walls. Isoniazid is a prodrug that is activated by KatG, the mycobacterial catalase-peroxidase. The activated form of isoniazid forms a covalent complex with an acyl carrier protein (AcpM) and KasA, a beta-ketoacyl carrier protein synthetase, which blocks mycolic acid synthesis and kills the cell. Resistance to isoniazid is associated with mutations resulting in overexpression of *inhA*, which encodes an NADH-dependent acyl carrier protein reductase; mutation or deletion of the *katG* gene; promoter mutations resulting in overexpression of *ahpC*, a putative virulence gene involved in protection of the cell from oxidative stress; and mutations in *kasA*. Overproducers of *inhA* express low-level isoniazid resistance and cross-resistance to ethionamide. *KatG* mutants express high-level isoniazid resistance and often are not cross-resistant to ethionamide.

Drug-resistant mutants are normally present in susceptible mycobacterial populations at about 1 bacillus in 10^6. Since tuberculous lesions often contain more than 10^8 tubercle bacilli, resistant mutants are readily selected if isoniazid or any other drug is given as a single agent. The use of two independently acting drugs in combination is much more effective. The probability that a bacillus is initially resistant to both drugs is approximately 1 in $10^6 \times 10^6$, or 1 in 10^{12}, several orders of magnitude greater than the number of infecting organisms. Thus, at least two (or more in certain cases) active agents should always be used to treat active tuberculosis to prevent emergence of resistance during therapy.

Pharmacokinetics

Isoniazid is readily absorbed from the gastrointestinal tract. A 300-mg oral dose (5 mg/kg in children) achieves peak plasma concentrations of 3–5 mcg/mL within 1–2 hours. Isoniazid diffuses readily into all body fluids and tissues. The concentration in the central nervous system and cerebrospinal fluid ranges between 20% and 100% of simultaneous serum concentrations.

Metabolism of isoniazid, especially acetylation by liver *N*-acetyltransferase, is genetically determined (see Chapter 4).

The average plasma concentration of isoniazid in rapid acetylators is about one third to one half of that in slow acetylators, and average half-lives are less than 1 hour and 3 hours, respectively. More rapid clearance of isoniazid by rapid acetylators is usually of no therapeutic consequence when appropriate doses are administered daily, but subtherapeutic concentrations may occur if drug is administered as a once-weekly dose or if there is malabsorption.

Isoniazid metabolites and a small amount of unchanged drug are excreted, mainly in the urine. The dose need not be adjusted in renal failure. Dose adjustment is not well defined in patients with severe preexisting hepatic insufficiency (isoniazid is contraindicated if it is the cause of the hepatitis) and should be guided by serum concentrations if a reduction in dose is contemplated.

Clinical Uses

The typical dosage of isoniazid is 5 mg/kg/d; a typical adult dose is 300 mg given once daily. Up to 10 mg/kg/d may be used for serious infections or if malabsorption is a problem. A 15 mg/kg dose, or 900 mg, may be used in a twice-weekly dosing regimen in combination with a second antituberculous agent (eg, rifampin 600 mg). Pyridoxine, 25–50 mg/d, is recommended for those with conditions predisposing to neuropathy, an adverse effect of isoniazid. Isoniazid is usually given by mouth but can be given parenterally in the same dosage.

Isoniazid as a single agent is also indicated for treatment of latent tuberculosis. The dosage is 300 mg/d (5 mg/kg/d) or 900 mg twice weekly for 9 months.

Adverse Reactions

The incidence and severity of untoward reactions to isoniazid are related to dosage and duration of administration.

A. Immunologic Reactions

Fever and skin rashes are occasionally seen. Drug-induced systemic lupus erythematosus has been reported.

B. Direct Toxicity

Isoniazid-induced hepatitis is the most common major toxic effect. This is distinct from the minor increases in liver aminotransferases (up to three or four times normal), which do not require cessation of the drug and which are seen in 10–20% of patients, who usually are asymptomatic. Clinical hepatitis with loss of appetite, nausea, vomiting, jaundice, and right upper quadrant pain occurs in 1% of isoniazid recipients and can be fatal, particularly if the drug is not discontinued promptly. There is histologic evidence of hepatocellular damage and necrosis. The risk of hepatitis depends on age. It occurs rarely under age 20, in 0.3% of those aged 21–35, 1.2% of those aged 36–50, and 2.3% for those aged 50 and above. The risk of hepatitis is greater in individuals with alcohol dependence and possibly during pregnancy and the postpartum period. Development of isoniazid hepatitis contraindicates further use of the drug.

Peripheral neuropathy is observed in 10–20% of patients given dosages greater than 5 mg/kg/d, but it is infrequently seen with the standard 300-mg adult dose. Peripheral neuropathy is more likely to occur in slow acetylators and patients with predisposing conditions such as malnutrition, alcoholism, diabetes, AIDS, and uremia. Neuropathy is due to a relative pyridoxine deficiency. Isoniazid promotes excretion of pyridoxine, and this toxicity is readily reversed by administration of pyridoxine in a dosage as low as 10 mg/d. Central nervous system toxicity, which is less common, includes memory loss, psychosis, and seizures. These effects may also respond to pyridoxine.

Miscellaneous other reactions include hematologic abnormalities, provocation of pyridoxine deficiency anemia, tinnitus, and gastrointestinal discomfort. Isoniazid can reduce the metabolism of phenytoin, increasing its blood level and toxicity.

RIFAMPIN

Rifampin is a semisynthetic derivative of rifamycin, an antibiotic produced by *Streptomyces mediterranei*. It is active in vitro against gram-positive and gram-negative cocci, some enteric bacteria, mycobacteria, and chlamydiae. Susceptible organisms are inhibited by less than 1 mcg/mL. Resistant mutants are present in all microbial populations at approximately 1 in 10^6 organisms and are rapidly selected out if rifampin is used as a single drug, especially in a patient with active infection. There is no cross-resistance to other classes of antimicrobial drugs, but there is cross-resistance to other rifamycin derivatives, eg, rifabutin and rifapentine.

Mechanism of Action, Resistance, & Pharmacokinetics

Rifampin binds to the β subunit of bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. Resistance results from any one of several possible point mutations in *rpoB*, the gene for the β subunit of RNA polymerase. These mutations result in reduced binding of rifampin to RNA polymerase. Human RNA polymerase does not bind rifampin and is not inhibited by it. Rifampin is bactericidal for mycobacteria. It readily penetrates most tissues and penetrates into phagocytic cells. It can kill organisms that are poorly accessible to many other drugs, such as intracellular organisms and those sequestered in abscesses and lung cavities.

Rifampin is well absorbed after oral administration and excreted mainly through the liver into bile. It then undergoes enterohepatic recirculation, with the bulk excreted as a deacylated metabolite in feces and a small amount excreted in the urine. Dosage adjustment for renal or hepatic insufficiency is not necessary. Usual doses result in serum levels of 5–7 mcg/mL. Rifampin is distributed widely in body fluids and tissues. The drug is relatively highly protein-bound, and adequate cerebrospinal fluid concentrations are achieved only in the presence of meningeal inflammation.

Clinical Uses

A. Mycobacterial Infections

Rifampin, usually 600 mg/d (10 mg/kg/d) orally, must be administered with isoniazid or other antituberculous drugs to patients with

active tuberculosis to prevent emergence of drug-resistant mycobacteria. In some short-course therapies, 600 mg of rifampin is given twice weekly. Rifampin, 600 mg daily or twice weekly for 6 months, also is effective in combination with other agents in some atypical mycobacterial infections and in leprosy. Rifampin, 600 mg daily for 4 months as a single drug, is an alternative to isoniazid for patients with latent tuberculosis who are unable to take isoniazid or who have had exposure to a case of active tuberculosis caused by an isoniazid-resistant, rifampin-susceptible strain.

B. Other Indications

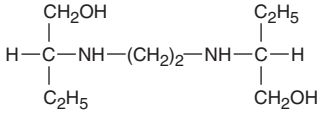
Rifampin has other uses in bacterial infections. An oral dosage of 600 mg twice daily for 2 days can eliminate meningococcal carriage. Rifampin, 20 mg/kg/d for 4 days, is used as prophylaxis in contacts of children with *Haemophilus influenzae* type b disease. Rifampin combined with a second agent is used to eradicate staphylococcal carriage. Rifampin combination therapy is also indicated for treatment of serious staphylococcal infections such as osteomyelitis and prosthetic valve endocarditis.

Adverse Reactions

Rifampin imparts a harmless orange color to urine, sweat, and tears (soft contact lenses may be permanently stained). Occasional adverse effects include rashes, thrombocytopenia, and nephritis. Rifampin may cause cholestatic jaundice and occasionally hepatitis, and it commonly causes light-chain proteinuria. If administered less often than twice weekly, rifampin may cause a flu-like syndrome characterized by fever, chills, myalgias, anemia, and thrombocytopenia. Its use has been associated with acute tubular necrosis. Rifampin strongly induces most cytochrome P450 isoforms (1A2, 2C9, 2C19, 2D6, and 3A4), which increases the elimination of numerous other drugs including methadone, anticoagulants, cyclosporine, some anticonvulsants, protease inhibitors, some nonnucleoside reverse transcriptase inhibitors, contraceptives, and a host of others (see Chapters 4 and 66). Co-administration of rifampin results in significantly lower serum levels of these drugs.

ETHAMBUTOL

Ethambutol is a synthetic, water-soluble, heat-stable compound, the dextro-isomer of the structure shown below, dispensed as the dihydrochloride salt.



Ethambutol

Mechanism of Action & Clinical Uses

Susceptible strains of *Mycobacterium tuberculosis* and other mycobacteria are inhibited in vitro by ethambutol, 1–5 mcg/mL. Ethambutol inhibits mycobacterial arabinosyl transferases, which are encoded by the *embCAB* operon. Arabinosyl transferases are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall. Resistance to ethambutol is due to mutations resulting in overexpression of *emb* gene products or within the *embB* structural gene.

Ethambutol is well absorbed from the gut. After ingestion of 25 mg/kg, a blood level peak of 2–5 mcg/mL is reached in 2–4 hours. About 20% of the drug is excreted in feces and 50% in urine in unchanged form. Ethambutol accumulates in renal failure, and the dose should be reduced by half if creatinine clearance is less than 10 mL/min. Ethambutol crosses the blood-brain barrier only when the meninges are inflamed. Concentrations in cerebrospinal fluid are highly variable, ranging from 4% to 64% of serum levels in the setting of meningeal inflammation.

As with all antituberculous drugs, resistance to ethambutol emerges rapidly when the drug is used alone. Therefore, ethambutol is always given in combination with other antituberculous drugs.

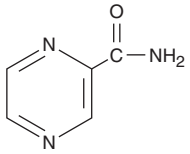
Ethambutol hydrochloride, 15–25 mg/kg, is usually given as a single daily dose in combination with isoniazid or rifampin. The higher dose is recommended for treatment of tuberculous meningitis. The dose of ethambutol is 50 mg/kg when a twice-weekly dosing schedule is used.

Adverse Reactions

Hypersensitivity to ethambutol is rare. The most common serious adverse event is retrobulbar neuritis, resulting in loss of visual acuity and red-green color blindness. This dose-related adverse effect is more likely to occur at dosages of 25 mg/kg/d continued for several months. At 15 mg/kg/d or less, visual disturbances are very rare. Periodic visual acuity testing is desirable if the 25 mg/kg/d dosage is used. Ethambutol is relatively contraindicated in children too young to permit assessment of visual acuity and red-green color discrimination.

PYRAZINAMIDE

Pyrazinamide (PZA) is a relative of nicotinamide. It is stable and slightly soluble in water. It is inactive at neutral pH, but at pH 5.5 it inhibits tubercle bacilli at concentrations of approximately 20 mcg/mL. The drug is taken up by macrophages and exerts its activity against mycobacteria residing within the acidic environment of lysosomes.



Pyrazinamide (PZA)

Mechanism of Action & Clinical Uses

Pyrazinamide is converted to pyrazinoic acid—the active form of the drug—by mycobacterial pyrazinamidase, which is encoded by

pncA. The specific drug target is unknown, but pyrazinoic acid disrupts mycobacterial cell membrane metabolism and transport functions. Resistance may be due to impaired uptake of pyrazinamide or mutations in *pncA* that impair conversion of pyrazinamide to its active form.

Serum concentrations of 30–50 mcg/mL at 1–2 hours after oral administration are achieved with dosages of 25 mg/kg/d. Pyrazinamide is well absorbed from the gastrointestinal tract and widely distributed in body tissues, including inflamed meninges. The half-life is 8–11 hours. The parent compound is metabolized by the liver, but metabolites are renally cleared; therefore, pyrazinamide should be administered at 25–35 mg/kg three times weekly (not daily) in hemodialysis patients and those in whom the creatinine clearance is less than 30 mL/min. In patients with normal renal function, a dose of 40–50 mg/kg is used for thrice-weekly or twice-weekly treatment regimens.

Pyrazinamide is an important front-line drug used in conjunction with isoniazid and rifampin in short-course (ie, 6-month) regimens as a "sterilizing" agent active against residual intracellular organisms that may cause relapse. Tubercle bacilli develop resistance to pyrazinamide fairly readily, but there is no cross-resistance with isoniazid or other antimycobacterial drugs.

Adverse Reactions

Major adverse effects of pyrazinamide include hepatotoxicity (in 1–5% of patients), nausea, vomiting, drug fever, and hyperuricemia. The latter occurs uniformly and is not a reason to halt therapy. Hyperuricemia may provoke acute gouty arthritis.

STREPTOMYCIN

The mechanism of action and other pharmacologic features of streptomycin are discussed in Chapter 45. The typical adult dose is 1 g/d (15 mg/kg/d). If the creatinine clearance is less than 30 mL/min or the patient is on hemodialysis, the dose is 15 mg/kg two or three times per week. Most tubercle bacilli are inhibited by streptomycin, 1–10 mcg/mL, in vitro. Nontuberculosis species of mycobacteria other than *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii* are resistant. All large populations of tubercle bacilli contain some streptomycin-resistant mutants. On average, 1 in 10^8 tubercle bacilli can be expected to be resistant to streptomycin at levels of 10–100 mcg/mL. Resistance is due to a point mutation in either the *rpsL* gene encoding the S12 ribosomal protein gene or the *rrs* gene encoding 16S ribosomal rRNA, which alters the ribosomal binding site.

Streptomycin penetrates into cells poorly and is active mainly against extracellular tubercle bacilli. Streptomycin crosses the blood-brain barrier and achieves therapeutic concentrations with inflamed meninges.

Clinical Use in Tuberculosis

Streptomycin sulfate is used when an injectable drug is needed or desirable and in the treatment of infections resistant to other drugs. The usual dosage is 15 mg/kg/d intramuscularly or intravenously daily for adults (20–40 mg/kg/d, not to exceed 1–1.5 g for children) for several weeks, followed by 1–1.5 g two or three times weekly for several months. Serum concentrations of approximately 40 mcg/mL are achieved 30–60 minutes after intramuscular injection of a 15 mg/kg dose. Other drugs are always given in combination to prevent emergence of resistance.

Adverse Reactions

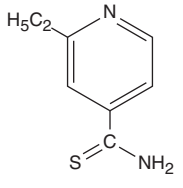
Streptomycin is ototoxic and nephrotoxic. Vertigo and hearing loss are the most common adverse effects and may be permanent. Toxicity is dose-related, and the risk is increased in the elderly. As with all aminoglycosides, the dose must be adjusted according to renal function (see Chapter 45). Toxicity can be reduced by limiting therapy to no more than 6 months whenever possible.

SECOND-LINE DRUGS FOR TUBERCULOSIS

The alternative drugs listed below are usually considered only (1) in case of resistance to first-line agents; (2) in case of failure of clinical response to conventional therapy; and (3) in case of serious treatment-limiting adverse drug reactions. Expert guidance to deal with the toxic effects of these second-line drugs is desirable. For many drugs listed in the following text, the dosage, emergence of resistance, and long-term toxicity have not been fully established.

Ethionamide

Ethionamide is chemically related to isoniazid and similarly blocks the synthesis of mycolic acids. It is poorly water soluble and available only in oral form. It is metabolized by the liver.



Ethionamide

Most tubercle bacilli are inhibited in vitro by ethionamide, 2.5 mcg/mL or less. Some other species of mycobacteria also are inhibited by ethionamide, 10 mcg/mL. Serum concentrations in plasma and tissues of approximately 20 mcg/mL are achieved by a dosage of 1 g/d. Cerebrospinal fluid concentrations are equal to those in serum.

Ethionamide is administered at an initial dose of 250 mg once daily, which is increased in 250-mg increments to the recommended dosage of 1 g/d (or 15 mg/kg/d), if possible. The 1 g/d dosage, though theoretically desirable, is poorly tolerated because of the intense gastric irritation and neurologic symptoms that commonly occur, and one often must settle for a total daily dose of 500–750 mg. Ethionamide is also hepatotoxic. Neurologic symptoms may be alleviated by pyridoxine.

Resistance to ethionamide as a single agent develops rapidly in vitro and in vivo. There can be low-level cross-resistance between isoniazid and ethionamide.

Capreomycin

Capreomycin is a peptide protein synthesis inhibitor antibiotic obtained from *Streptomyces capreolus*. Daily injection of 1 g intramuscularly results in blood levels of 10 mcg/mL or more. Such concentrations in vitro are inhibitory for many mycobacteria, including multidrug-resistant strains of *M tuberculosis*.

Capreomycin (15 mg/kg/d) is an important injectable agent for treatment of drug-resistant tuberculosis. Strains of *M tuberculosis* that are resistant to streptomycin or amikacin usually are susceptible to capreomycin. Resistance to capreomycin, when it occurs, may be due to an *rrs* mutation.

Capreomycin is nephrotoxic and ototoxic. Tinnitus, deafness, and vestibular disturbances occur. The injection causes significant local pain, and sterile abscesses may occur.

Dosing of capreomycin is the same as that of streptomycin. Toxicity is reduced if 1 g is given two or three times weekly after an initial response has been achieved with a daily dosing schedule.

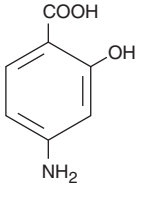
Cycloserine

Cycloserine is an inhibitor of cell wall synthesis and is discussed in Chapter 43. Concentrations of 15–20 mcg/mL inhibit many strains of *M tuberculosis*. The dosage of cycloserine in tuberculosis is 0.5–1 g/d in two divided oral doses. Cycloserine is cleared renally, and the dose should be reduced by half if creatinine clearance is less than 50 mL/min.

The most serious toxic effects are peripheral neuropathy and central nervous system dysfunction, including depression and psychotic reactions. Pyridoxine, 150 mg/d, should be given with cycloserine because this ameliorates neurologic toxicity. Adverse effects, which are most common during the first 2 weeks of therapy, occur in 25% or more of patients, especially at higher doses. Adverse effects can be minimized by monitoring peak serum concentrations. The peak concentration is reached 2–4 hours after dosing. The recommended range of peak concentrations is 20–40 mcg/mL.

Aminosalicylic Acid (PAS)

Aminosalicylic acid is a folate synthesis antagonist that is active almost exclusively against *M tuberculosis*. It is structurally similar to *p*-aminobenzoic acid (PABA) and to the sulfonamides (see Chapter 46).



Aminosalicylic acid (PAS)

Tubercle bacilli are usually inhibited in vitro by aminosalicylic acid, 1–5 mcg/mL. Aminosalicylic acid is readily absorbed from the gastrointestinal tract. Serum levels are 50 mcg/mL or more after a 4-g oral dose. The dosage is 8–12 g/d orally for adults and 300 mg/kg/d for children. The drug is widely distributed in tissues and body fluids except the cerebrospinal fluid. Aminosalicylic acid is rapidly excreted in the urine, in part as active aminosalicylic acid and in part as the acetylated compound and other metabolic products. Very high concentrations of aminosalicylic acid are reached in the urine, which can result in crystalluria.

Aminosalicylic acid is used infrequently because other oral drugs are better tolerated. Gastrointestinal symptoms are common and may be diminished by giving the drug with meals and with antacids. Peptic ulceration and hemorrhage may occur. Hypersensitivity reactions manifested by fever, joint pains, skin rashes, hepatosplenomegaly, hepatitis, adenopathy, and granulocytopenia often occur after 3–8 weeks of aminosalicylic acid therapy, making it necessary to stop aminosalicylic acid administration temporarily or permanently.

Kanamycin & Amikacin

The aminoglycoside antibiotics are discussed in Chapter 45. Kanamycin has been used for treatment of tuberculosis caused by streptomycin-resistant strains, but the availability of less toxic alternatives (eg, capreomycin and amikacin) has rendered it obsolete.

The role of amikacin in treatment of tuberculosis has increased with the increasing incidence and prevalence of multidrug-resistant tuberculosis. Prevalence of amikacin-resistant strains is low (< 5%), and most multidrug-resistant strains remain amikacin-susceptible. *M tuberculosis* is inhibited at concentrations of 1 mcg/mL or less. Amikacin is also active against atypical mycobacteria. There is no cross-resistance between streptomycin and amikacin, but kanamycin resistance often indicates resistance to amikacin as well. Serum concentrations of 30–50 mcg/mL are achieved 30–60 minutes after a 15 mg/kg intravenous infusion. Amikacin is indicated for treatment of tuberculosis suspected or known to be caused by streptomycin-resistant or multidrug-resistant strains. Amikacin must be used in combination with at least one and preferably two or three other drugs to which the isolate is susceptible for treatment of drug-resistant cases. The recommended dosages are the same as those for streptomycin.

Fluoroquinolones

In addition to their activity against many gram-positive and gram-negative bacteria (discussed in Chapter 46), ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin inhibit strains of *M tuberculosis* at concentrations less than 2 mcg/mL. They are also active against atypical mycobacteria. Moxifloxacin is the most active against *M tuberculosis* by weight in vitro. Levofloxacin tends to be slightly more active than ciprofloxacin against *M tuberculosis*, whereas ciprofloxacin is slightly more active against atypical mycobacteria.

Fluoroquinolones are an important addition to the drugs available for tuberculosis, especially for strains that are resistant to first-line agents. Resistance, which may result from any one of several single point mutations in the gyrase A subunit, develops rapidly if a fluoroquinolone is used as a single agent; thus, the drug must be used in combination with two or more other active

agents. The standard dosage of ciprofloxacin is 750 mg orally twice a day. The dosage of levofloxacin is 500–750 mg once a day. The dosage of moxifloxacin is 400 mg once a day.

Linezolid

Linezolid (discussed in Chapter 44) inhibits strains of *M tuberculosis* in vitro at concentrations of 4–8 mcg/mL. It achieves good intracellular concentrations, and it is active in murine models of tuberculosis. Linezolid has been used in combination with other second- and third-line drugs to treat patients with tuberculosis caused by multidrug-resistant strains. Conversion of sputum cultures to negative was associated with linezolid use in these cases, and some may have been cured. Significant and at times treatment-limiting adverse effects, including bone marrow suppression and irreversible peripheral and optic neuropathy, have been reported with the prolonged courses of therapy that are necessary for treatment of tuberculosis. A 600-mg (adult) dose administered once a day (half of that used for treatment of other bacterial infections) seems to be sufficient and may limit the occurrence of these adverse effects. Although linezolid may eventually prove to be an important new agent for treatment of tuberculosis, at this point it should be considered a drug of last resort for infection caused by multidrug-resistant strains that also are resistant to several other first- and second-line agents.

Rifabutin

Rifabutin is derived from rifamycin and is related to rifampin. It has significant activity against *M tuberculosis*, MAC, and *Mycobacterium fortuitum* (see below). Its activity is similar to that of rifampin, and cross-resistance with rifampin is virtually complete. Some rifampin-resistant strains may appear susceptible to rifabutin in vitro, but a clinical response is unlikely because the molecular basis of resistance, *rpoB* mutation, is the same. Rifabutin is both substrate and inducer of cytochrome P450 enzymes. Because it is a less potent inducer, rifabutin is indicated in place of rifampin for treatment of tuberculosis in patients with HIV infection who are receiving antiretroviral therapy with a protease inhibitor or with a nonnucleoside reverse transcriptase inhibitor (eg, efavirenz), drugs that also are cytochrome P450 substrates.

The typical dosage of rifabutin is 300 mg/d unless the patient is receiving a protease inhibitor, in which case the dosage should be reduced to 150 mg/d. If efavirenz (also a cytochrome P450 inducer) is used, the recommended dosage of rifabutin is 450 mg/d.

Rifabutin is effective in prevention and treatment of disseminated atypical mycobacterial infection in AIDS patients with CD4 counts below 50/μL. It is also effective for preventive therapy of tuberculosis, either alone in a 3–4 month regimen or with pyrazinamide in a 2-month regimen.

Rifapentine

Rifapentine is an analog of rifampin. It is active against both *M tuberculosis* and MAC. As with all rifamycins, it is a bacterial RNA polymerase inhibitor, and cross-resistance between rifampin and rifapentine is complete. Like rifampin, rifapentine is a potent inducer of cytochrome P450 enzymes, and it has the same drug interaction profile. Toxicity is similar to that of rifampin. Rifapentine and its microbiologically active metabolite, 25-desacetylrifapentine, have an elimination half-life of 13 hours. Rifapentine, 600 mg (10 mg/kg) once weekly, is indicated for treatment of tuberculosis caused by rifampin-susceptible strains during the continuation phase only (ie, after the first 2 months of therapy and ideally after conversion of sputum cultures to negative). Rifapentine should not be used to treat patients with HIV infection because of an unacceptably high relapse rate with rifampin-resistant organisms.

RIFAXIMIN

Rifaximin is a rifampin derivative that is not absorbed from the gastrointestinal tract. It is approved for oral administration in the prevention of hepatic encephalopathy and for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients 12 years of age and older. It has also been used off label for irritable bowel syndrome and for *Clostridium difficile* colitis not responsive to other drugs.

DRUGS ACTIVE AGAINST ATYPICAL MYCOBACTERIA

About 10% of mycobacterial infections seen in clinical practice in the United States are caused by nontuberculous or "atypical" mycobacteria. These organisms have distinctive laboratory characteristics, are present in the environment, and are generally not communicable from person to person. As a rule, these mycobacterial species are less susceptible than *M tuberculosis* to antituberculous drugs. On the other hand, agents such as erythromycin, sulfonamides, or tetracycline, which are not active against *M tuberculosis*, may be effective for infections caused by atypical mycobacteria. Emergence of resistance during therapy is also a problem with these mycobacterial species, and active infection should be treated with combinations of drugs. *M kansasii* is susceptible to rifampin and ethambutol, partially resistant to isoniazid, and completely resistant to pyrazinamide. A three-drug combination of isoniazid, rifampin, and ethambutol is the conventional treatment for *M kansasii* infection. A few representative pathogens, with the clinical presentation and the drugs to which they are often susceptible, are given in Table 47–3.

M avium complex (MAC), which includes both *M avium* and *M intracellulare*, is an important and common cause of disseminated disease in late stages of AIDS (CD4 counts < 50/μL). MAC is much less susceptible than *M tuberculosis* to most antituberculous drugs. Combinations of agents are required to suppress the infection. Azithromycin, 500 mg once daily, or clarithromycin, 500 mg twice daily, plus ethambutol, 15–25 mg/kg/d, is an effective and well-tolerated regimen for treatment of disseminated disease. Some authorities recommend use of a third agent, such as ciprofloxacin, 750 mg twice daily, or rifabutin, 300 mg once daily. Other agents that may be useful are listed in Table 47–3. Azithromycin and clarithromycin are the drugs of choice for reducing the incidence of MAC

TABLE 47–3 Clinical features and treatment options for infections with atypical mycobacteria.

Species	Clinical Features	Treatment Options
M kansasii	Resembles tuberculosis	Ciprofloxacin, clarithromycin, ethambutol, isoniazid, rifampin, trimethoprim-sulfamethoxazole
M marinum	Granulomatous cutaneous disease	Amikacin, clarithromycin, ethambutol, doxycycline, minocycline, rifampin, trimethoprim-sulfamethoxazole
M scrofulaceum	Cervical adenitis in children	Amikacin, erythromycin (or other macrolide), rifampin, streptomycin (Surgical excision is often curative and the treatment of choice.)
M avium complex	Pulmonary disease in patients with chronic lung disease; disseminated infection in AIDS	Amikacin, azithromycin, clarithromycin, ciprofloxacin, ethambutol, rifabutin
M chelonae	Abscess, sinus tract, ulcer; bone, joint, tendon infection	Amikacin, doxycycline, imipenem, macrolides, tobramycin
M fortuitum	Abscess, sinus tract, ulcer; bone, joint, tendon infection	Amikacin, cefoxitin, ciprofloxacin, doxycycline, ofloxacin, trimethoprim-sulfamethoxazole
M ulcerans	Skin ulcers	Isoniazid, streptomycin, rifampin, minocycline (Surgical excision may be effective.)

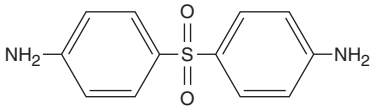
bacteremia in AIDS patients with CD4 cell counts less than 100/μL. Rifabutin in a single daily dose of 300 mg has been shown to reduce the incidence of MAC bacteremia but is less effective than macrolides.

■ DRUGS USED IN LEPROSY

Mycobacterium leprae has never been grown in vitro, but animal models, such as growth in injected mouse footpads, have permitted laboratory evaluation of drugs. Only those drugs with the widest clinical use are presented here. Because of increasing reports of dapsone resistance, treatment of leprosy with combinations of the drugs listed below is recommended.

DAPSONE & OTHER SULFONES

Several drugs closely related to the sulfonamides have been used effectively in the long-term treatment of leprosy. The most widely used is dapsone (diaminodiphenylsulfone). Like the sulfonamides, it inhibits folate synthesis. Resistance can emerge in large populations of *M leprae*, eg, in lepromatous leprosy, if very low doses are given. Therefore, the combination of dapsone, rifampin, and clofazimine is recommended for initial therapy. Dapsone may also be used to prevent and treat *Pneumocystis jiroveci* pneumonia in AIDS patients.



Dapsone

Sulfones are well absorbed from the gut and widely distributed throughout body fluids and tissues. Dapsone's half-life is 1–2 days, and drug tends to be retained in skin, muscle, liver, and kidney. Skin heavily infected with *M leprae* may contain several times more drug than normal skin. Sulfones are excreted into bile and reabsorbed in the intestine. Excretion into urine is variable, and most excreted drug is acetylated. In renal failure, the dose may have to be adjusted. The usual adult dosage in leprosy is 100 mg daily. For children, the dose is proportionately less, depending on weight.

Dapsone is usually well tolerated. Many patients develop some hemolysis, particularly if they have glucose-6-phosphate dehydrogenase deficiency. Methemoglobinemia is common, but usually is not a problem clinically. Gastrointestinal intolerance, fever, pruritus, and various rashes occur. During dapsone therapy of lepromatous leprosy, erythema nodosum leprosum often develops. It is sometimes difficult to distinguish reactions to dapsone from manifestations of the underlying illness. Erythema nodosum leprosum may be suppressed by **corticosteroids** or by **thalidomide**.

RIFAMPIN

Rifampin (see earlier discussion) in a dosage of 600 mg daily is highly effective in lepromatous leprosy. Because of the probable risk of emergence of rifampin-resistant *M leprae*, the drug is given in combination with dapsone or another antileprosy drug. A single monthly dose of 600 mg may be beneficial in combination therapy.

CLOFAZIMINE

Clofazimine is a phenazine dye that can be used as an alternative to dapsone. Its mechanism of action is unknown but may involve DNA binding.

Absorption of clofazimine from the gut is variable, and a major portion of the drug is excreted in feces. Clofazimine is stored widely in reticuloendothelial tissues and skin, and its crystals can be seen inside phagocytic reticuloendothelial cells. It is slowly released from these deposits, so that the serum half-life may be 2 months.

Clofazimine is given for sulfone-resistant leprosy or when patients are intolerant to sulfones. A common dosage is 100 mg/d orally. The most prominent untoward effect is skin discoloration ranging from red-brown to nearly black. Gastrointestinal intolerance occurs occasionally.

SUMMARY First-Line Antimycobacterial Drugs

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ISONIAZID	Inhibits synthesis of mycolic acids, an essential component of mycobacterial cell walls	Bactericidal activity against susceptible strains of *M tuberculosis*	First-line agent for tuberculosis • treatment of latent infection • less active against other mycobacteria	Oral, IV • hepatic clearance (half-life 1 h) • reduces levels of phenytoin • *Toxicity:* Hepatotoxic, peripheral neuropathy (give pyridoxine to prevent)
RIFAMYCINS				
• Rifampin	Inhibits DNA-dependent RNA polymerase, thereby blocking production of RNA	Bactericidal activity against susceptible bacteria and mycobacteria • resistance rapidly emerges when used as a single drug in the treatment of active infection	First-line agent for tuberculosis • atypical mycobacterial infections • eradication of meningococcal colonization, staphylococcal infections	Oral, IV • hepatic clearance (half-life 3.5 h) • potent cytochrome P450 inducer • turns body fluids orange color • *Toxicity:* Rash, nephritis, thrombocytopenia, cholestasis, flu-like syndrome with intermittent dosing
• *Rifabutin: Oral; similar to rifampin but less cytochrome P450 induction and fewer drug interactions*				
• *Rifapentine: Oral; long-acting analog of rifampin that may be given once weekly in the continuation phase of tuberculosis treatment*				
PYRAZINAMIDE	Not fully understood • pyrazinamide is converted to the active pyrazinoic acid under acidic conditions in macrophage lysosomes	Bacteriostatic activity against susceptible strains of *M tuberculosis* • may be bactericidal against actively dividing organisms	"Sterilizing" agent used during first 2 months of therapy • allows total duration of therapy to be shortened to 6 months	Oral • hepatic clearance (half-life 9 h), but metabolites are renally cleared so use doses 3 × weekly if creatinine clearance < 30 mL/min • *Toxicity:* Hepatotoxic, hyperuricemia
ETHAMBUTOL	Inhibits mycobacterial arabinosyl transferases, which are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall	Bacteriostatic activity against susceptible mycobacteria	Given in four-drug initial combination therapy for tuberculosis until drug sensitivities are known • also used for atypical mycobacterial infections	Oral • mixed clearance (half-life 4 h) • dose must be reduced in renal failure • *Toxicity:* Retrobulbar neuritis
STREPTOMYCIN	Prevents bacterial protein synthesis by binding to the S12 ribosomal subunit (see also Chapter 45)	Bactericidal activity against susceptible mycobacteria	Used in tuberculosis when an injectable drug is needed or desirable and in treatment of drug-resistant strains	IM, IV • renal clearance (half-life 2.5 h) • administered daily initially, then 2 × week • *Toxicity:* Nephrotoxic, ototoxic

PREPARATIONS AVAILABLE[1]

DRUGS USED IN TUBERCULOSIS

Aminosalicylate sodium (Paser)
Oral: 4 g delayed-release granules

Capreomycin (Capastat Sulfate)
Parenteral: 1 g powder to reconstitute for injection

Cycloserine (Seromycin Pulvules)
Oral: 250 mg capsules

Ethambutol (Myambutol)
Oral: 100, 400 mg tablets

Ethionamide (Trecator-SC)
Oral: 250 mg tablets

Isoniazid (generic)
Oral: 100, 300 mg tablets; syrup, 50 mg/5 mL
Parenteral: 100 mg/mL for injection

Pyrazinamide (generic)
Oral: 500 mg tablets

Rifabutin (Mycobutin)
Oral: 150 mg capsules

Rifampin (generic, Rifadin, Rimactane)
Oral: 150, 300 mg capsules
Parenteral: 600 mg powder for IV injection

Rifapentine (Priftin)
Oral: 150 mg tablets

Rifaximin (Xifaxan)
Oral: 200, 550 mg tablets

Streptomycin (generic)
Parenteral: 1 g lyophilized for IM injection

DRUGS USED IN LEPROSY

Clofazimine (Lamprene)
Oral: 50 mg capsules

Dapsone (generic)
Oral: 25, 100 mg tablets

[1]Drugs used against atypical mycobacteria are listed in Chapters 43–46.

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CASE STUDY ANSWER

The patient should be started on four-drug therapy with rifampin, isoniazid, pyrazinamide, and ethambutol. If a protease-inhibitor-based antiretroviral regimen is used to treat his HIV, rifabutin should replace rifampin because of the serious drug-drug interaction between rifampin and protease inhibitors. The patient is at increased risk of developing hepatotoxicity from both isoniazid and pyrazinamide given his history of chronic alcohol dependence.

CHAPTER

48

Antifungal Agents

Don Sheppard, MD, & Harry W. Lampiris, MD

CASE STUDY

A 55-year-old man presents to the emergency department with a 2-week history of an expanding ulcer on his left lower leg. He has a history of chronic neutropenia and transfusion-dependent anemia secondary to myelodysplastic syndrome requiring chronic therapy with deferoxamine for hepatic iron overload. He first noticed a red bump on his leg while fishing at his cabin in the woods and thought it was a bug bite. It rapidly enlarged, first as a red swollen area, and then began to ulcerate. He was given dicloxacillin orally, but with no improvement. In the emergency department he is febrile to 39°C (102.2°F), and looks unwell. On his left leg he has a 6 by 12 cm black ulcer with surrounding swelling and erythema that is quite tender. His complete blood count demonstrates an absolute neutrophil count of 300 and a total white blood cell count of 1000. An immediate operative debridement yields pathologic specimens demonstrating broad club-like nonseptate hyphae and extensive tissue necrosis. What initial medical therapy would be most appropriate?

Human fungal infections have increased dramatically in incidence and severity in recent years, owing mainly to advances in surgery, cancer treatment, treatment of patients with solid organ and bone marrow transplantation, the HIV epidemic, and increasing use of broad-spectrum antimicrobial therapy in critically ill patients. These changes have resulted in increased numbers of patients at risk for fungal infections.

For many years, **amphotericin B** was the only efficacious antifungal drug available for systemic use. While highly effective in many serious infections, it is also quite toxic. In the last several decades, pharmacotherapy of fungal disease has been revolutionized by the introduction of the relatively nontoxic **azole** drugs (both oral and parenteral formulations) and the **echinocandins** (only available for parenteral administration). The new agents in these classes offer more targeted, less toxic therapy than older agents such as amphotericin B for patients with serious systemic fungal infections. Combination therapy is being reconsidered, and new formulations of old agents are becoming available. Unfortunately, the appearance of azole-resistant organisms, as well as the rise in the number of patients at risk for mycotic infections, has created new challenges.

The antifungal drugs presently available fall into the following categories: systemic drugs (oral or parenteral) for systemic infections, oral systemic drugs for mucocutaneous infections, and topical drugs for mucocutaneous infections.

SYSTEMIC ANTIFUNGAL DRUGS FOR SYSTEMIC INFECTIONS

AMPHOTERICIN B

Amphotericin A and B are antifungal antibiotics produced by *Streptomyces nodosus*. Amphotericin A is not in clinical use.

Chemistry & Pharmacokinetics

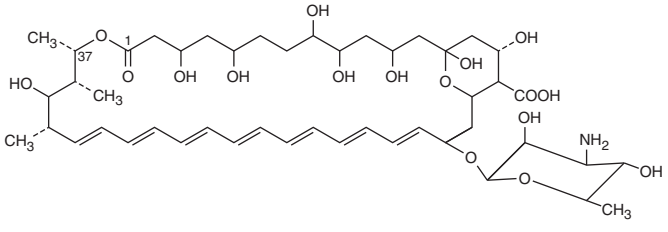
Amphotericin B is an amphoteric polyene macrolide (polyene = containing many double bonds; macrolide = containing a large lactone ring of 12 or more atoms). It is nearly insoluble in water and is therefore prepared as a colloidal suspension of amphotericin B and sodium desoxycholate for intravenous injection. Several formulations have been developed in which amphotericin B is

TABLE 48–1 Properties of conventional amphotericin B and some lipid formulations.[1]

Drug	Physical Form	Dosing (mg/kg/d)	C_{max}	Clearance	Nephrotoxicity	Infusional Toxicity	Daily Cost ($)
Conventional formulation							
Fungizone	Micelles	1	…	…	…	…	24
Lipid formulations							
AmBisome	Spheres	3–5	↑	↓	↓	↓	1300
Amphotec	Disks	5	↓	↑	↓	↑(?)	660
Abelcet	Ribbons	5	↓	↑	↓	↓(?)	570

[1]Changes in C_{max} (peak plasma concentration), clearance, nephrotoxicity, and infusional toxicity are relative to conventional amphotericin B.

packaged in a lipid-associated delivery system (Table 48–1 and Box: Liposomal Amphotericin B).



Amphotericin B

Amphotericin B is poorly absorbed from the gastrointestinal tract. Oral amphotericin B is thus effective only on fungi within the lumen of the tract and cannot be used for treatment of systemic disease. The intravenous injection of 0.6 mg/kg/d of amphotericin B results in average blood levels of 0.3–1 mcg/mL; the drug is more than 90% bound by serum proteins. Although it is mostly metabolized, some amphotericin B is excreted slowly in the urine over a period of several days. The serum half-life is approximately 15 days. Hepatic impairment, renal impairment, and dialysis have little impact on drug concentrations, and therefore no dose adjustment is required. The drug is widely distributed in most tissues, but only 2–3% of the blood level is reached in cerebrospinal fluid, thus occasionally necessitating intrathecal therapy for certain types of fungal meningitis.

Mechanisms of Action & Resistance

Amphotericin B is selective in its fungicidal effect because it exploits the difference in lipid composition of fungal and mammalian cell membranes. **Ergosterol,** a cell membrane sterol, is found in the cell membrane of fungi, whereas the predominant sterol of bacteria and human cells is **cholesterol.** Amphotericin B binds to ergosterol and alters the permeability of the cell by forming amphotericin B-associated pores in the cell membrane (Figure 48–1). As suggested by its chemistry, amphotericin B combines avidly with

Liposomal Amphotericin B

Therapy with amphotericin B is often limited by toxicity, especially drug-induced renal impairment. This has led to the development of lipid drug formulations on the assumption that lipid-packaged drug binds to the mammalian membrane less readily, permitting the use of effective doses of the drug with lower toxicity. Liposomal amphotericin preparations package the active drug in lipid delivery vehicles, in contrast to the colloidal suspensions, which were previously the only available forms. Amphotericin binds to the lipids in these vehicles with an affinity between that for fungal ergosterol and that for human cholesterol. The lipid vehicle then serves as an amphotericin reservoir, reducing nonspecific binding to human cell membranes. This preferential binding allows for a reduction of toxicity without sacrificing efficacy and permits use of larger doses. Furthermore, some fungi contain lipases that may liberate free amphotericin B directly at the site of infection.

Three such formulations are now available and have differing pharmacologic properties as summarized in Table 48–1. Although clinical trials have demonstrated different renal and infusion-related toxicities for these preparations compared with regular amphotericin B, there are no trials comparing the different formulations with each other. Limited studies have suggested at best a moderate improvement in the clinical efficacy of the lipid formulations compared with conventional amphotericin B. Because the lipid preparations are much more expensive, their use is usually restricted to patients intolerant to, or not responding to, conventional amphotericin treatment.

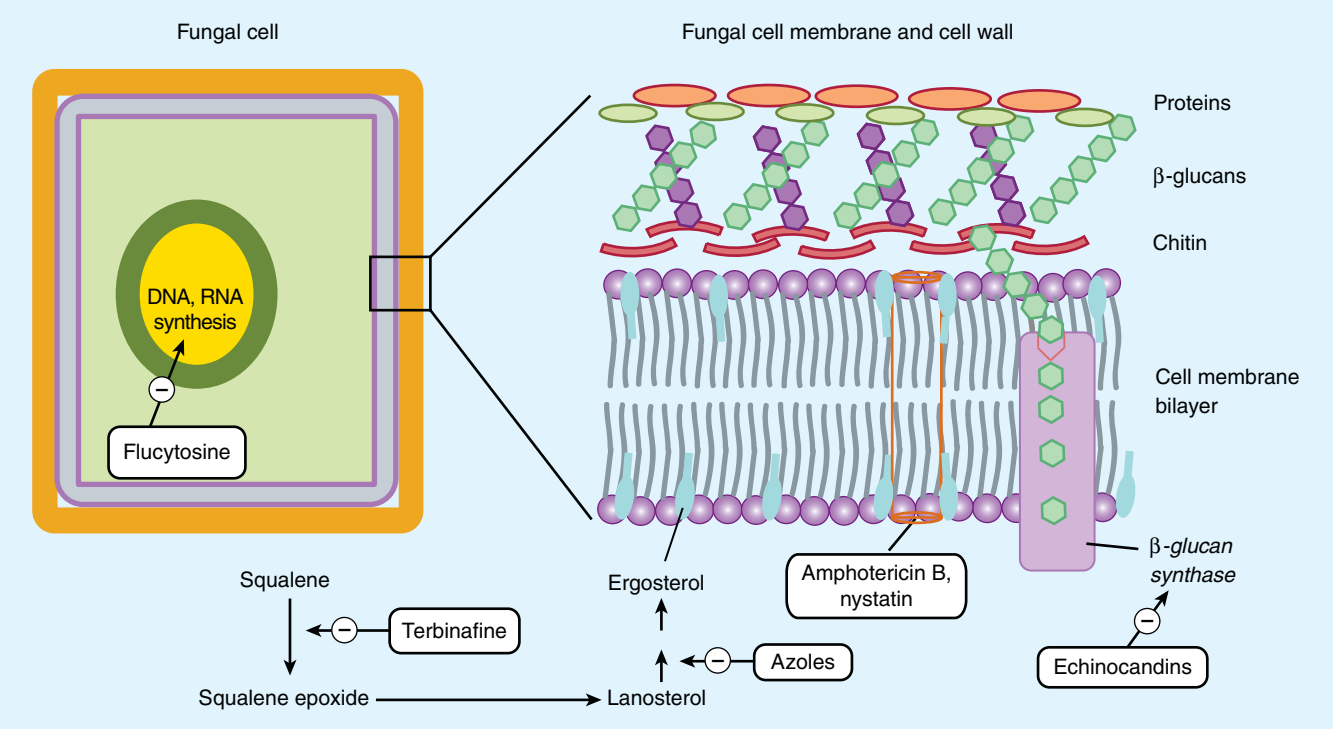


FIGURE 48–1 Targets of antifungal drugs. Except for flucytosine (and possibly griseofulvin, not shown), all currently available antifungals target the fungal cell membrane or cell wall.

lipids (ergosterol) along the double bond-rich side of its structure and associates with water molecules along the hydroxyl-rich side. This amphipathic characteristic facilitates pore formation by multiple amphotericin molecules, with the lipophilic portions around the outside of the pore and the hydrophilic regions lining the inside. The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death. Some binding to human membrane sterols does occur, probably accounting for the drug's prominent toxicity.

Resistance to amphotericin B occurs if ergosterol binding is impaired, either by decreasing the membrane concentration of ergosterol or by modifying the sterol target molecule to reduce its affinity for the drug.

Antifungal Activity & Clinical Uses

Amphotericin B remains the antifungal agent with the broadest spectrum of action. It has activity against the clinically significant yeasts, including *Candida albicans* and *Cryptococcus neoformans*; the organisms causing endemic mycoses, including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*; and the pathogenic molds, such as *Aspergillus fumigatus* and the agents of mucormycosis. Some fungal organisms such as *Candida lusitaniae* and *Pseudallescheria boydii* display intrinsic amphotericin B resistance.

Owing to its broad spectrum of activity and fungicidal action, amphotericin B remains a useful agent for nearly all life-threatening mycotic infections, although newer, less toxic agents have largely replaced it for most conditions. Amphotericin B is often used as the initial induction regimen to rapidly reduce fungal burden and then replaced by one of the newer azole drugs (described below) for chronic therapy or prevention of relapse. Such induction therapy is especially important for immunosuppressed patients and those with severe fungal pneumonia, severe cryptococcal meningitis, or disseminated infections with one of the endemic mycoses such as histoplasmosis or coccidioidomycosis. Once a clinical response has been elicited, these patients then often continue maintenance therapy with an azole; therapy may be lifelong in patients at high risk for disease relapse. For treatment of systemic fungal disease, amphotericin B is given by slow intravenous infusion at a dosage of 0.5–1 mg/kg/d. It is usually continued to a defined total dose (eg, 1–2 g), rather than a defined time span, as used with other antimicrobial drugs.

Intrathecal therapy for fungal meningitis is poorly tolerated and fraught with difficulties related to maintaining cerebrospinal fluid access. Thus, intrathecal therapy with amphotericin B is being increasingly supplanted by other therapies but remains an option in cases of fungal central nervous system infections that have not responded to other agents.

Local or topical administration of amphotericin B has been used with success. Mycotic corneal ulcers and keratitis can be cured with topical drops as well as by direct subconjunctival injection. Fungal arthritis has been treated with adjunctive local injection

directly into the joint. Candiduria responds to bladder irrigation with amphotericin B, and this route has been shown to produce no significant systemic toxicity.

Adverse Effects

The toxicity of amphotericin B can be divided into two broad categories: immediate reactions, related to the infusion of the drug, and those occurring more slowly.

A. Infusion-Related Toxicity

Infusion-related reactions are nearly universal and consist of fever, chills, muscle spasms, vomiting, headache, and hypotension. They can be ameliorated by slowing the infusion rate or decreasing the daily dose. Premedication with antipyretics, antihistamines, meperidine, or corticosteroids can be helpful. When starting therapy, many clinicians administer a test dose of 1 mg intravenously to gauge the severity of the reaction. This can serve as a guide to an initial dosing regimen and premedication strategy.

B. Cumulative Toxicity

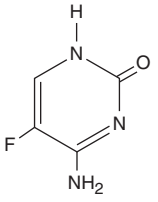
Renal damage is the most significant toxic reaction. Renal impairment occurs in nearly all patients treated with clinically significant doses of amphotericin. The degree of azotemia is variable and often stabilizes during therapy, but it can be serious enough to necessitate dialysis. A reversible component is associated with decreased renal perfusion and represents a form of prerenal renal failure. An irreversible component results from renal tubular injury and subsequent dysfunction. The irreversible form of amphotericin nephrotoxicity usually occurs in the setting of prolonged administration (> 4 g cumulative dose). Renal toxicity commonly manifests as renal tubular acidosis and severe potassium and magnesium wasting. There is some evidence that the prerenal component can be attenuated with sodium loading, and it is common practice to administer normal saline infusions with the daily doses of amphotericin B.

Abnormalities of liver function tests are occasionally seen, as is a varying degree of anemia due to reduced erythropoietin production by damaged renal tubular cells. After intrathecal therapy with amphotericin, seizures and a chemical arachnoiditis may develop, often with serious neurologic sequelae.

FLUCYTOSINE

Chemistry & Pharmacokinetics

Flucytosine (5-FC) was discovered in 1957 during a search for novel antineoplastic agents. Though devoid of anticancer properties, it became apparent that it was a potent antifungal agent. Flucytosine is a water-soluble pyrimidine analog related to the chemotherapeutic agent 5-fluorouracil (5-FU). Its spectrum of action is much narrower than that of amphotericin B.



Flucytosine

Flucytosine is currently available in North America only in an oral formulation. The dosage is 100–150 mg/kg/d in patients with normal renal function. It is well absorbed (> 90%), with serum concentrations peaking 1–2 hours after an oral dose. It is poorly protein-bound and penetrates well into all body fluid compartments, including the cerebrospinal fluid. It is eliminated by glomerular filtration with a half-life of 3–4 hours and is removed by hemodialysis. Levels rise rapidly with renal impairment and can lead to toxicity. Toxicity is more likely to occur in AIDS patients and those with renal insufficiency. Peak serum concentrations should be measured periodically in patients with renal insufficiency and maintained between 50 and 100 mcg/mL.

Mechanisms of Action & Resistance

Flucytosine is taken up by fungal cells via the enzyme cytosine permease. It is converted intracellularly first to 5-FU and then to 5-fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP), which inhibit DNA and RNA synthesis, respectively (Figure 48–1). Human cells are unable to convert the parent drug to its active metabolites, resulting in selective toxicity.

Synergy with amphotericin B has been demonstrated in vitro and in vivo. It may be related to enhanced penetration of the flucytosine through amphotericin-damaged fungal cell membranes. In vitro synergy with azole drugs has also been seen, although the mechanism is unclear.

Resistance is thought to be mediated through altered metabolism of flucytosine, and, though uncommon in primary isolates, it develops rapidly in the course of flucytosine monotherapy.

Clinical Uses & Adverse Effects

The spectrum of activity of flucytosine is restricted to *C neoformans*, some *Candida* sp, and the dematiaceous molds that cause chromoblastomycosis. Flucytosine is not used as a single agent because of its demonstrated synergy with other agents and to avoid the development of secondary resistance. Clinical use at present is confined to combination therapy, either with amphotericin B for cryptococcal meningitis or with itraconazole for chromoblastomycosis.

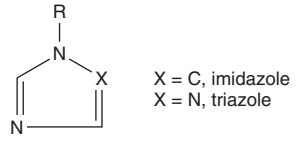
The adverse effects of flucytosine result from metabolism (possibly by intestinal flora) to the toxic antineoplastic compound fluorouracil. Bone marrow toxicity with anemia, leukopenia, and thrombocytopenia are the most common adverse effects, with derangement of liver enzymes occurring less frequently. A form of toxic enterocolitis can occur. There seems to be a narrow therapeutic window, with an increased risk of toxicity at higher drug levels and

resistance developing rapidly at subtherapeutic concentrations. The use of drug concentration measurements may be helpful in reducing the incidence of toxic reactions, especially when flucytosine is combined with nephrotoxic agents such as amphotericin B.

AZOLES

Chemistry & Pharmacokinetics

Azoles are synthetic compounds that can be classified as either imidazoles or triazoles according to the number of nitrogen atoms in the five-membered azole ring, as indicated below. The imidazoles consist of ketoconazole, miconazole, and clotrimazole (Figure 48–2). The latter two drugs are now used only in topical therapy. The triazoles include itraconazole, fluconazole, voriconazole, and posaconazole.



Azole nucleus

The pharmacology of each of the azoles is unique and accounts for some of the variations in clinical use. Table 48–2 summarizes the differences among five of the azoles.

Mechanisms of Action & Resistance

The antifungal activity of azole drugs results from the reduction of ergosterol synthesis by inhibition of fungal cytochrome P450 enzymes (Figure 48–1). The selective toxicity of azole drugs results

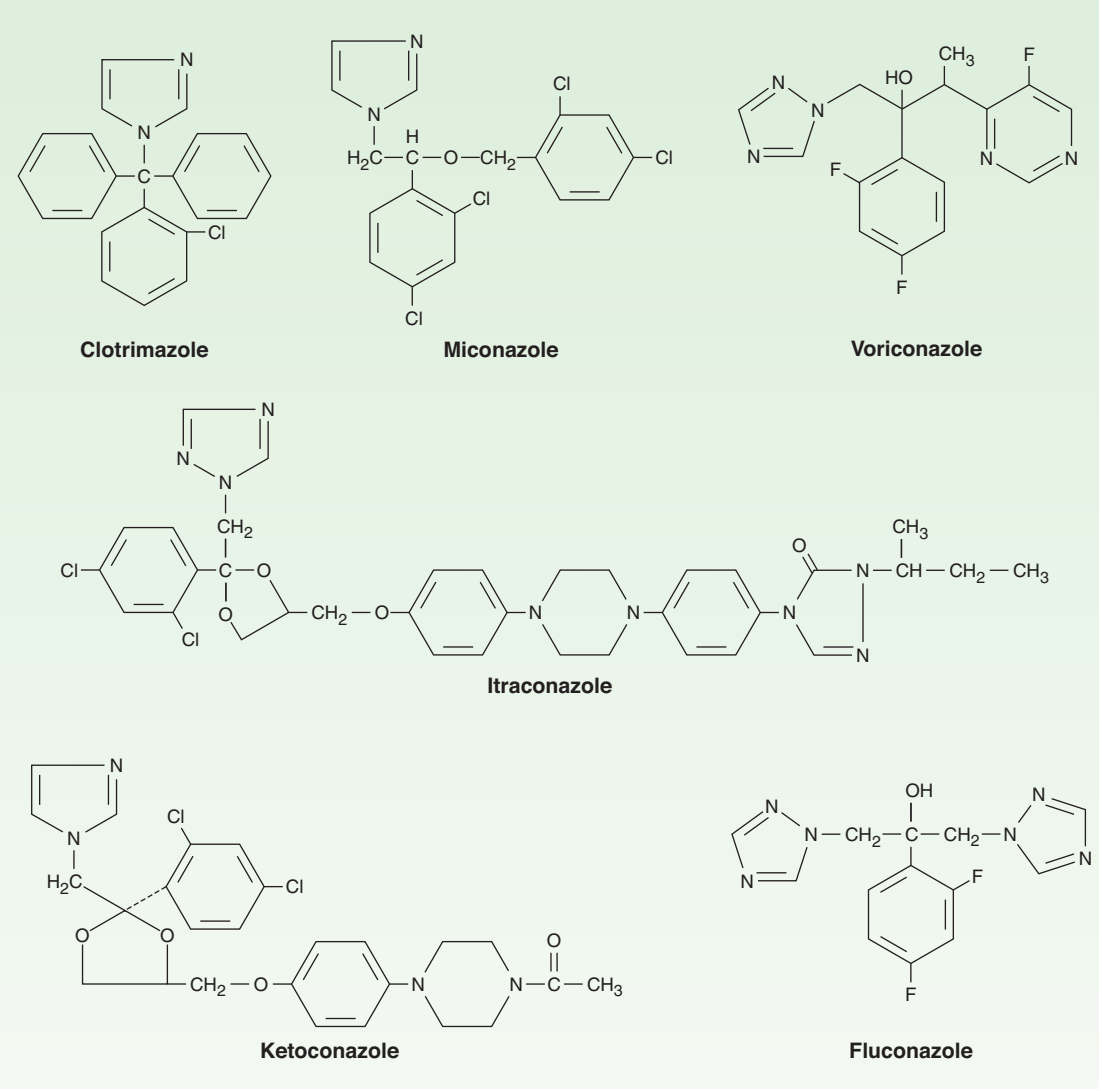


FIGURE 48–2 Structural formulas of some antifungal azoles.

TABLE 48–2 Pharmacologic properties of five systemic azole drugs.

	Water Solubility	Absorption	CSF: Serum Concentration Ratio	$t_{½}$ (hours)	Elimination	Formulations
Ketoconazole	Low	Variable	< 0.1	7–10	Hepatic	Oral
Itraconazole	Low	Variable	< 0.01	24–42	Hepatic	Oral, IV
Fluconazole	High	High	> 0.7	22–31	Renal	Oral, IV
Voriconazole	High	High	…	6	Hepatic	Oral, IV
Posaconazole	Low	High	…	25	Hepatic	Oral

from their greater affinity for fungal than for human cytochrome P450 enzymes. Imidazoles exhibit a lesser degree of selectivity than the triazoles, accounting for their higher incidence of drug interactions and adverse effects.

Resistance to azoles occurs via multiple mechanisms. Once rare, increasing numbers of resistant strains are being reported, suggesting that increasing use of these agents for prophylaxis and therapy may be selecting for clinical drug resistance in certain settings.

Clinical Uses, Adverse Effects, & Drug Interactions

The spectrum of action of azole medications is broad, including many species of *Candida, C neoformans*, the endemic mycoses (blastomycosis, coccidioidomycosis, histoplasmosis), the dermatophytes, and, in the case of itraconazole and voriconazole, even *Aspergillus* infections. They are also useful in the treatment of intrinsically amphotericin-resistant organisms such as *P boydii.*

As a group, the azoles are relatively nontoxic. The most common adverse reaction is relatively minor gastrointestinal upset. All azoles have been reported to cause abnormalities in liver enzymes and, very rarely, clinical hepatitis. Adverse effects specific to individual agents are discussed below.

All azole drugs are prone to drug interactions because they affect the mammalian cytochrome P450 system of enzymes to some extent. The most significant reactions are indicated below.

KETOCONAZOLE

Ketoconazole was the first oral azole introduced into clinical use. It is distinguished from triazoles by its greater propensity to inhibit mammalian cytochrome P450 enzymes; that is, it is less selective for fungal P450 than are the newer azoles. As a result, systemic ketoconazole has fallen out of clinical use in the USA and is not discussed in any detail here. Its dermatologic use is discussed in Chapter 61.

ITRACONAZOLE

Itraconazole is available in oral and intravenous formulations and is used at a dosage of 100–400 mg/d. Drug absorption is increased by food and by low gastric pH. Like other lipid-soluble azoles, it interacts with hepatic microsomal enzymes, though to a lesser degree than ketoconazole. An important drug interaction is reduced bioavailability of itraconazole when taken with rifamycins (rifampin, rifabutin, rifapentine). It does not affect mammalian steroid synthesis, and its effects on the metabolism of other hepatically cleared medications are much less than those of ketoconazole. While itraconazole displays potent antifungal activity, effectiveness can be limited by reduced bioavailability. Newer formulations, including an oral liquid and an intravenous preparation, have utilized cyclodextran as a carrier molecule to enhance solubility and bioavailability. Like ketoconazole, itraconazole penetrates poorly into the cerebrospinal fluid. Itraconazole is the azole of choice for treatment of disease due to the dimorphic fungi *Histoplasma, Blastomyces*, and *Sporothrix.* Itraconazole has activity against *Aspergillus* sp, but it has been replaced by voriconazole as the azole of choice for aspergillosis. Itraconazole is used extensively in the treatment of dermatophytoses and onychomycosis.

FLUCONAZOLE

Fluconazole displays a high degree of water solubility and good cerebrospinal fluid penetration. Unlike ketoconazole and itraconazole, its oral bioavailability is high. Drug interactions are also less common because fluconazole has the least effect of all the azoles on hepatic microsomal enzymes. Because of fewer hepatic enzyme interactions and better gastrointestinal tolerance, fluconazole has the widest therapeutic index of the azoles, permitting more aggressive dosing in a variety of fungal infections. The drug is available in oral and intravenous formulations and is used at a dosage of 100–800 mg/d.

Fluconazole is the azole of choice in the treatment and secondary prophylaxis of cryptococcal meningitis. Intravenous fluconazole has been shown to be equivalent to amphotericin B in treatment of candidemia in ICU patients with normal white blood cell counts. Fluconazole is the agent most commonly used for the treatment of mucocutaneous candidiasis. Activity against the dimorphic fungi is limited to coccidioidal disease, and in particular for meningitis, where high doses of fluconazole often obviate the need for intrathecal amphotericin B. Fluconazole displays no activity against *Aspergillus* or other filamentous fungi.

Prophylactic use of fluconazole has been demonstrated to reduce fungal disease in bone marrow transplant recipients and AIDS patients, but the emergence of fluconazole-resistant fungi has raised concerns about this indication.

VORICONAZOLE

Voriconazole is available in intravenous and oral formulations. The recommended dosage is 400 mg/d. The drug is well absorbed orally, with a bioavailability exceeding 90%, and it exhibits less protein binding than itraconazole. Metabolism is predominantly hepatic. Voriconazole is a clinically relevant inhibitor of mammalian CYP3A4, and dose reduction of a number of medications is required when voriconazole is started. These include cyclosporine, tacrolimus, and HMG-CoA reductase inhibitors. Observed toxicities include rash and elevated hepatic enzymes. Visual disturbances are common, occurring in up to 30% of patients receiving intravenous voriconazole, and include blurring and changes in color vision or brightness. These visual changes usually occur immediately after a dose of voriconazole and resolve within 30 minutes. Photosensitivity dermatitis is commonly observed in patients receiving chronic oral therapy.

Voriconazole is similar to itraconazole in its spectrum of action, having excellent activity against *Candida* sp (including fluconazole-resistant species such as *Candida krusei*) and the dimorphic fungi. Voriconazole is less toxic than amphotericin B and is the treatment of choice for invasive aspergillosis.

POSACONAZOLE

Posaconazole is the newest triazole to be licensed in the USA. It is available only in a liquid oral formulation and is used at a dosage of 800 mg/d, divided into two or three doses. Absorption is improved when taken with meals high in fat. Posaconazole is rapidly distributed to the tissues, resulting in high tissue levels but relatively low blood levels. Visual changes have not been reported, but drug interactions with increased levels of CYP3A4 substrates such as tacrolimus and cyclosporine have been documented.

Posaconazole is the broadest spectrum member of the azole family, with activity against most species of *Candida* and *Aspergillus*. It is the only azole with significant activity against the agents of mucormycosis. It is currently licensed for salvage therapy in invasive aspergillosis, as well as prophylaxis of fungal infections during induction chemotherapy for leukemia, and for allogeneic bone marrow transplant patients with graft-versus-host disease.

ECHINOCANDINS

Chemistry & Pharmacokinetics

Echinocandins are the newest class of antifungal agents to be developed. They are large cyclic peptides linked to a long-chain fatty acid. **Caspofungin, micafungin,** and **anidulafungin** are the only licensed agents in this category of antifungals, although other drugs are under active investigation. These agents are active against *Candida* and *Aspergillus,* but not *C neoformans* or the agents of zygomycosis and mucormycosis.

Echinocandins are available only in intravenous formulations. Caspofungin is administered as a single loading dose of 70 mg, followed by a daily dose of 50 mg. Caspofungin is water soluble and highly protein-bound. The half-life is 9–11 hours, and the metabolites are excreted by the kidneys and gastrointestinal tract. Dosage adjustments are required only in the presence of severe hepatic insufficiency. Micafungin displays similar properties with a half-life of 11–15 hours and is used at a dose of 150 mg/d for treatment of esophageal candidiasis, 100 mg/d for treatment of candidemia, and 50 mg/d for prophylaxis of fungal infections. Anidulafungin has a half-life of 24–48 hours. For esophageal candidiasis, it is administered intravenously at 100 mg on the first day and 50 mg/d thereafter for 14 days. For candidemia, a loading dose of 200 mg is recommended with 100 mg/d thereafter for at least 14 days after the last positive blood culture.

Mechanism of Action

Echinocandins act at the level of the fungal cell wall by inhibiting the synthesis of β(1–3)-glucan (Figure 48–1). This results in disruption of the fungal cell wall and cell death.

Clinical Uses & Adverse Effects

Caspofungin is currently licensed for disseminated and mucocutaneous candidal infections, as well as for empiric antifungal therapy during febrile neutropenia, and has largely replaced amphotericin B for the latter indication. Of note, caspofungin is licensed for use in invasive aspergillosis only as salvage therapy in patients who have failed to respond to amphotericin B, and not as primary therapy. Micafungin is licensed for mucocutaneous candidiasis, candidemia, and prophylaxis of candidal infections in bone marrow transplant patients. Anidulafungin is approved for use in esophageal candidiasis and invasive candidiasis, including candidemia.

Echinocandin agents are extremely well tolerated, with minor gastrointestinal side effects and flushing reported infrequently. Elevated liver enzymes have been noted in several patients receiving caspofungin in combination with cyclosporine, and this combination should be avoided. Micafungin has been shown to increase levels of nifedipine, cyclosporine, and sirolimus. Anidulafungin does not seem to have significant drug interactions, but histamine release may occur during intravenous infusion.

■ ORAL SYSTEMIC ANTIFUNGAL DRUGS FOR MUCOCUTANEOUS INFECTIONS

GRISEOFULVIN

Griseofulvin is a very insoluble fungistatic drug derived from a species of penicillium. Its only use is in the systemic treatment of dermatophytosis (see Chapter 61). It is administered in a microcrystalline form at a dosage of 1 g/d. Absorption is improved when

it is given with fatty foods. Griseofulvin's mechanism of action at the cellular level is unclear, but it is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection. Because its action is to prevent infection of these new skin structures, griseofulvin must be administered for 2–6 weeks for skin and hair infections to allow the replacement of infected keratin by the resistant structures. Nail infections may require therapy for months to allow regrowth of the new protected nail and is often followed by relapse. Adverse effects include an allergic syndrome much like serum sickness, hepatitis, and drug interactions with warfarin and phenobarbital. Griseofulvin has been largely replaced by newer antifungal medications such as itraconazole and terbinafine.

TERBINAFINE

Terbinafine is a synthetic allylamine that is available in an oral formulation and is used at a dosage of 250 mg/d. It is used in the treatment of dermatophytoses, especially onychomycosis (see Chapter 61). Like griseofulvin, terbinafine is a keratophilic medication, but unlike griseofulvin, it is fungicidal. Like the azole drugs, it interferes with ergosterol biosynthesis, but rather than interacting with the P450 system, terbinafine inhibits the fungal enzyme squalene epoxidase (Figure 48–1). This leads to the accumulation of the sterol squalene, which is toxic to the organism. One tablet given daily for 12 weeks achieves a cure rate of up to 90% for onychomycosis and is more effective than griseofulvin or itraconazole. Adverse effects are rare, consisting primarily of gastrointestinal upset and headache. Terbinafine does not seem to affect the P450 system and has demonstrated no significant drug interactions to date.

■ TOPICAL ANTIFUNGAL THERAPY

NYSTATIN

Nystatin is a polyene macrolide much like amphotericin B. It is too toxic for parenteral administration and is only used topically. Nystatin is currently available in creams, ointments, suppositories, and other forms for application to skin and mucous membranes. It is not absorbed to a significant degree from skin, mucous membranes, or the gastrointestinal tract. As a result, nystatin has little toxicity, although oral use is often limited by the unpleasant taste.

Nystatin is active against most *Candida* sp and is most commonly used for suppression of local candidal infections. Some common indications include oropharyngeal thrush, vaginal candidiasis, and intertriginous candidal infections.

TOPICAL AZOLES

The two azoles most commonly used topically are clotrimazole and miconazole; several others are available (see Preparations Available). Both are available over-the-counter and are often used for vulvovaginal candidiasis. Oral clotrimazole troches are available for treatment of oral thrush and are a pleasant-tasting alternative to nystatin. In cream form, both agents are useful for dermatophytic infections, including tinea corporis, tinea pedis, and tinea cruris. Absorption is negligible, and adverse effects are rare.

Topical and shampoo forms of ketoconazole are also available and useful in the treatment of seborrheic dermatitis and pityriasis versicolor. Several other azoles are available for topical use (see Preparations Available).

TOPICAL ALLYLAMINES

Terbinafine and naftifine are allylamines available as topical creams (see Chapter 61). Both are effective for treatment of tinea cruris and tinea corporis. These are prescription drugs in the USA.

SUMMARY Antifungal Drugs

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
POLYENE MACROLIDE				
• Amphotericin B	Forms pores in fungal membranes (which contain ergosterol) but not in mammalian (cholesterol-containing) membranes	Loss of intracellular contents through pores is fungicidal • broad spectrum of action	Localized and systemic candidemia • *Cryptococcus* • *Histoplasma* • *Blastomyces* • *Coccidioides* • *Aspergillus*	Oral but not absorbed • IV for systemic use • intrathecal for fungal meningitis • topical for ocular and bladder infections • duration, days • *Toxicity:* Infusion reactions • renal impairment • *Interactions:* Additive with other renal toxic drugs
• *Lipid formulations: Lower toxicity, higher doses can be used*				
PYRIMIDINE ANALOG				
• Flucytosine	Interferes with DNA and RNA synthesis selectively in fungi	Synergistic with amphotericin • systemic toxicity in host due to DNA and RNA effects	*Cryptococcus* and chromoblastomycosis infections	Oral • duration, hours • renal excretion • *Toxicity:* Myelosuppression
AZOLES				
• Ketoconazole	Blocks fungal P450 enzymes and interferes with ergosterol synthesis	Poorly selective • interferes with mammalian P450 function	Broad spectrum but toxicity restricts use to topical therapy	Oral, topical • *Toxicity and interactions:* Interferes with steroid hormone synthesis and phase I drug metabolism
• Itraconazole	Same as for ketoconazole	Much more selective than ketoconazole	Broad spectrum: *Candida, Cryptococcus,* blastomycosis, coccidioidomycosis, histoplasmosis	Oral and IV • duration, 1–2 d • poor entry into central nervous system (CNS) • *Toxicity and interactions:* Low toxicity
• *Fluconazole, voriconazole, posaconazole: Fluconazole has excellent CNS penetration, used in fungal meningitis*				
ECHINOCANDINS				
• Caspofungin	Blocks β-glucan synthase	Prevents synthesis of fungal cell wall	Fungicidal *Candida sp* • also used in aspergillosis	IV only • duration, 11–15 h • *Toxicity:* Minor gastrointestinal effects, flushing • *Interactions:* Increases cyclosporine levels (avoid combination)
• *Micafungin, anidulafungin: Micafungin increases levels of nifedipine, cyclosporine, sirolimus; anidulafungin is relatively free of this interaction*				
ALLYLAMINE				
• Terbinafine	Inhibits epoxidation of squalene in fungi • increased levels are toxic to them	Reduces ergosterol • prevents synthesis of fungal cell membrane	Mucocutaneous fungal infections	Oral • duration, days • *Toxicity:* Gastrointestinal upset, headache, hepatotoxicity • *Interactions:* None reported

PREPARATIONS AVAILABLE

Amphotericin B
Parenteral:
Conventional formulation (Amphotericin B, Fungizone): 50 mg powder for injection
Lipid formulations:
(Abelcet): 100 mg/20 mL suspension for injection
(AmBisome): 50 mg powder for injection
(Amphotec): 50, 100 mg powder for injection
Topical: 3% cream, lotion, ointment

Anidulafungin (Eraxis)
Parenteral: 50 mg powder for injection

Butenafine (Lotrimin Ultra, Mentax)
Topical: 1% cream

Butoconazole (Gynazole-1, Mycelex-3)
Topical: 2% vaginal cream

Caspofungin (Cancidas)
Parenteral: 50, 70 mg powder for injection

Clotrimazole (generic, Lotrimin)
Topical: 1% cream, solution, lotion; 100, 200 mg vaginal suppositories

Econazole (generic, Spectazole)
Topical: 1% cream

Fluconazole (Diflucan)
Oral: 50, 100, 150, 200 mg tablets; powder for 10, 40 mg/mL suspension
Parenteral: 2 mg/mL in 100 and 200 mL vials

Flucytosine (Ancobon)
Oral: 250, 500 mg capsules

Griseofulvin (Grifulvin, Grisactin, Fulvicin P/G)
Oral microsize: 125, 250 mg tablets; 250 mg capsule, 125 mg/5 mL suspension
Oral ultramicrosize:[1] 125, 165, 250, 330 mg tablets

Itraconazole (Sporanox)
Oral: 100 mg capsules; 10 mg/mL solution
Parenteral: 10 mg/mL for IV infusion

Ketoconazole (generic, Nizoral)
Oral: 200 mg tablets
Topical: 2% cream, shampoo

Micafungin (Mycamine)
Parenteral: 50 mg powder for injection

Miconazole (generic, Micatin)
Topical: 2% cream, powder, spray; 100, 200 mg vaginal suppositories

Naftifine (Naftin)
Topical: 1% cream, gel

Natamycin (Natacyn)
Topical: 5% ophthalmic suspension

Nystatin (generic, Mycostatin)
Oral: 500,000 unit tablets
Topical: 100,000 units/g cream, ointment, powder; 100,000 units vaginal tablets

Oxiconazole (Oxistat)
Topical: 1% cream, lotion

Posaconazole (Noxafil)
Oral: suspension 40 mg/mL

Sulconazole (Exelderm)
Topical: 1% cream, solution

Terbinafine (Lamisil)
Oral: 250 mg tablets
Topical: 1% cream, gel

Terconazole (Terazol 3, Terazol 7)
Topical: 0.4%, 0.8% vaginal cream; 80 mg vaginal suppositories

Tioconazole (Vagistat-1, Monistat 1)
Topical: 6.5% vaginal ointment

Tolnaftate (generic, Aftate, Tinactin)
Topical: 1% cream, gel, solution, aerosol powder

Voriconazole (Vfend)
Oral: 50, 200 mg tablets; oral suspension 40 mg/mL
Parenteral: 200 mg vials, reconstituted to a 5 mg/mL solution

[1]Ultramicrosize formulations of griseofulvin are approximately 1.5 times more potent, milligram for milligram, than the microsize preparations.

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CASE STUDY ANSWER

The club-like nonseptate hyphae observed in cultures of intraoperative specimens from this patient are characteristic of *Rhizopus*, one of the agents of mucormycosis. This patient should be treated with an initial, prolonged course of therapy with liposomal amphotericin B and caspofungin and subsequent chronic suppressive therapy with posaconazole.

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CHAPTER 49

Antiviral Agents

Sharon Safrin, MD

CASE STUDY

A 35-year-old white woman who recently tested seropositive for both HIV and hepatitis B virus surface antigen is referred for evaluation. She is feeling well overall but reports a 25-pack-year smoking history. She drinks 3–4 beers per week and has no known medication allergies. She has a history of heroin use and is currently receiving methadone. Physical examination reveals normal vital signs and no abnormalities. White blood cell count is 5800 cells/mm^3 with a normal differential, hemoglobin is 11.8 g/dL, all liver function tests are within normal limits, CD4 cell count is 278 cells/mm^3, and viral load (HIV RNA) is 110,000 copies/mL. What other laboratory tests should be ordered? Which antiretroviral medications would you begin?

Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cell. Therefore, to be effective, antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell. As a corollary, nonselective inhibitors of virus replication may interfere with host cell function and result in toxicity.

Progress in antiviral chemotherapy began in the early 1950s, when the search for anticancer drugs generated several new compounds capable of inhibiting viral DNA synthesis. The two first-generation antiviral agents, 5-iododeoxyuridine and trifluorothymidine, had poor specificity (ie, they inhibited host cell DNA as well as viral DNA) that rendered them too toxic for systemic use. However, both agents are effective when used topically for the treatment of herpes keratitis.

Knowledge of the mechanisms of viral replication has provided insights into critical steps in the viral life cycle that can serve as potential targets for antiviral therapy. Recent research has focused on identifying agents with greater selectivity, higher potency, in vivo stability, and reduced toxicity. Antiviral therapy is now available for herpesviruses, hepatitis C virus (HCV), hepatitis B virus (HBV), papillomavirus, influenza, and human immunodeficiency virus (HIV). Antiviral drugs share the common property of being virustatic; they are active only against replicating viruses and do not affect latent virus. Whereas some infections require monotherapy for brief periods of time (eg, acyclovir for herpes simplex virus), others require dual therapy for prolonged periods of time (interferon alfa/ribavirin for HCV), whereas still others require multiple drug therapy for indefinite periods (HIV). In chronic illnesses such

ACRONYMS & OTHER NAMES

3TC	Lamivudine
AZT	Zidovudine (previously azidothymidine)
CMV	Cytomegalovirus
CYP	Cytochrome P450
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
EBV	Epstein-Barr virus
FTC	Emtricitabine
HBeAg	Hepatitis e antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHV-6	Human herpesvirus-6
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
PI	Protease inhibitor
RSV	Respiratory syncytial virus
SVR	Sustained viral response
UGT1A1	UDP-glucuronosyl transferase 1A1
VZV	Varicella-zoster virus

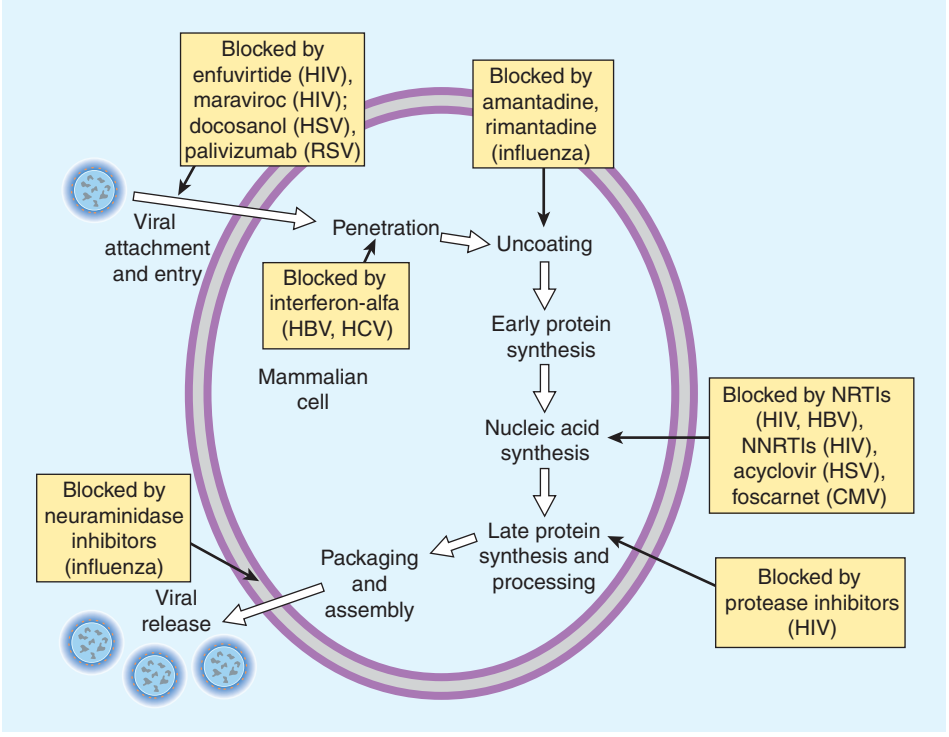

FIGURE 49–1 The major sites of antiviral drug action. Note: Interferon alfas are speculated to have multiple sites of action. (Modified and reproduced, with permission, from Trevor AJ, Katzung BG, Masters SB: *Pharmacology: Examination & Board Review,* 9th ed. McGraw-Hill, 2010.)

as viral hepatitis and HIV infection, potent inhibition of viral replication is crucial in limiting the extent of systemic damage.

Viral replication requires several steps (Figure 49–1): (1) attachment of the virus to receptors on the host cell surface; (2) entry of the virus through the host cell membrane; (3) uncoating of viral nucleic acid; (4) synthesis of early regulatory proteins, eg, nucleic acid polymerases; (5) synthesis of new viral RNA or DNA; (6) synthesis of late, structural proteins; (7) assembly (maturation) of viral particles; and (8) release from the cell. Antiviral agents can potentially target any of these steps.

■ AGENTS TO TREAT HERPES SIMPLEX VIRUS (HSV) & VARICELLA-ZOSTER VIRUS (VZV) INFECTIONS

Three oral nucleoside analogs are licensed for the treatment of HSV and VZV infections: acyclovir, valacyclovir, and famciclovir. They have similar mechanisms of action and comparable indications for clinical use; all are well tolerated. Acyclovir has been the most extensively studied; it was licensed first and is the only one of the three that is available for intravenous use in the United States. Comparative trials have demonstrated similar efficacies of these three agents for the treatment of HSV but modest superiority of famciclovir and valacyclovir for the treatment of herpes zoster infections.

ACYCLOVIR

Acyclovir (Figure 49–2) is an acyclic guanosine derivative with clinical activity against HSV-1, HSV-2, and VZV, but it is approximately 10 times more potent against HSV-1 and HSV-2 than against VZV. In vitro activity against Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus-6 (HHV-6) is present but weaker.

Acyclovir requires three phosphorylation steps for activation. It is converted first to the monophosphate derivative by the virus-specified thymidine kinase and then to the di- and triphosphate compounds by host cell enzymes (Figure 49–3). Because it requires the viral kinase for initial phosphorylation, acyclovir is selectively activated—and the active metabolite accumulates—only in infected cells. Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms: competition with deoxyGTP for the viral DNA polymerase, resulting in binding to the DNA template as an irreversible complex; and chain termination following incorporation into the viral DNA.

The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food. An intravenous formulation is available. Topical formulations produce high concentrations in herpetic lesions, but systemic concentrations are undetectable by this route.

Acyclovir is cleared primarily by glomerular filtration and tubular secretion. The half-life is 2.5–3 hours in patients with normal renal function and 20 hours in patients with anuria.

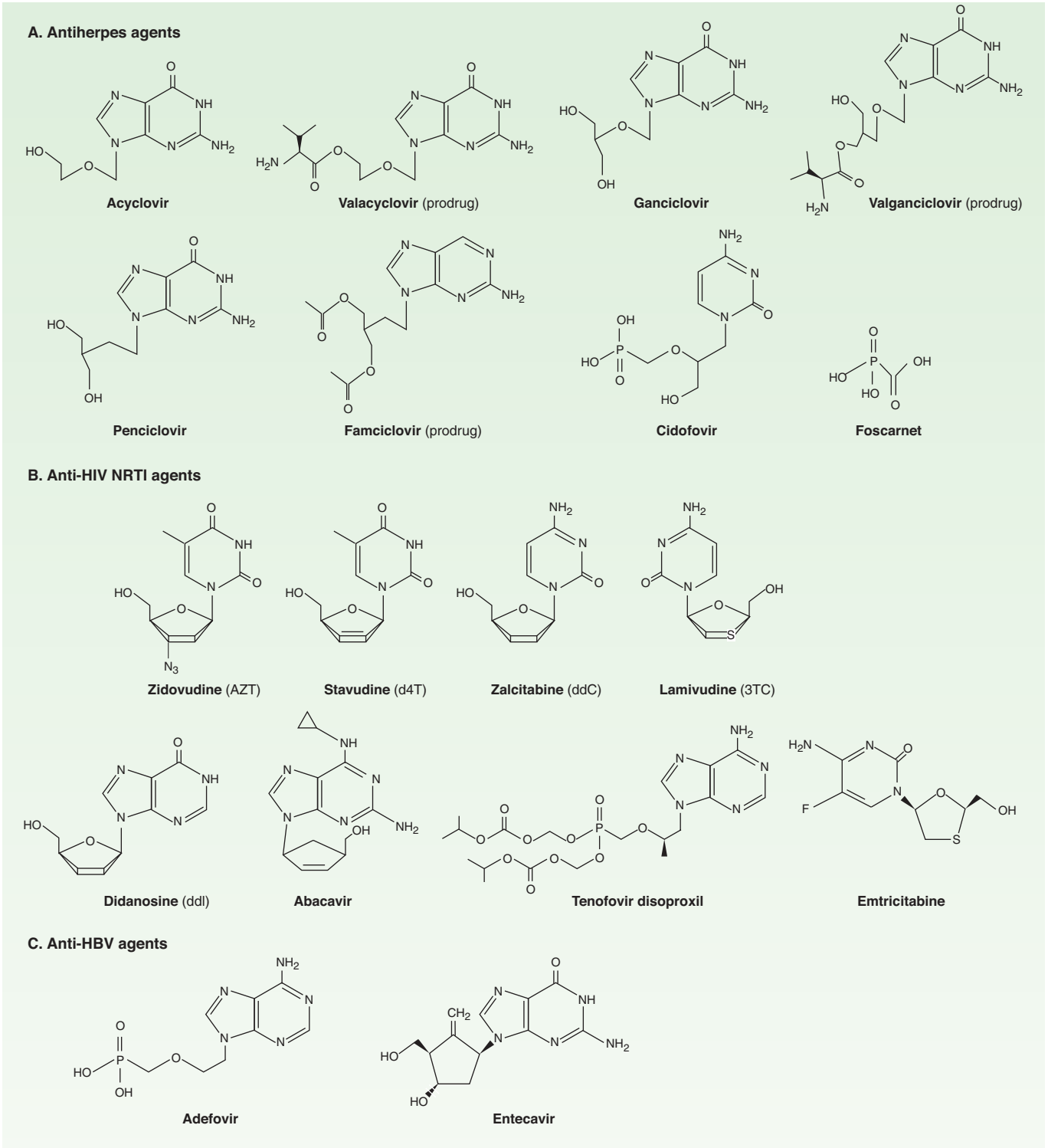

FIGURE 49–2 Chemical structures of some antiviral nucleoside and nucleotide analogs.

Acyclovir diffuses readily into most tissues and body fluids. Cerebrospinal fluid concentrations are 20–50% of serum values.

Oral acyclovir has multiple uses. In first episodes of genital herpes, oral acyclovir shortens the duration of symptoms by approximately 2 days, the time to lesion healing by 4 days, and the duration of viral shedding by 7 days. In recurrent genital herpes, the time course is shortened by 1–2 days. Treatment of first-episode genital herpes does not alter the frequency or severity of recurrent outbreaks. Long-term suppression with oral acyclovir in patients with frequent recurrences of genital herpes decreases the

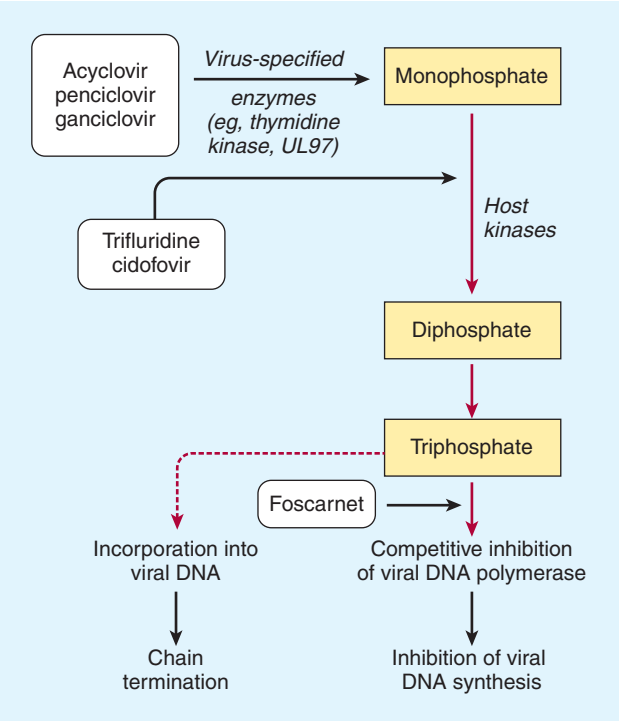

FIGURE 49–3 Mechanism of action of antiherpes agents.

frequency of symptomatic recurrences and of asymptomatic viral shedding, thus decreasing the rate of sexual transmission. However, outbreaks may resume upon discontinuation of suppressive acyclovir. Oral acyclovir is only modestly beneficial in recurrent herpes labialis. In contrast, acyclovir therapy significantly decreases the total number of lesions, duration of symptoms, and viral shedding in patients with varicella (if begun within 24 hours after the onset of rash) or cutaneous zoster (if begun within 72 hours). However, because VZV is less susceptible to acyclovir than HSV, higher doses are required (Table 49–1). When given prophylactically to patients undergoing organ transplantation, oral or intravenous acyclovir prevents reactivation of HSV infection. Evidence from recent clinical trials suggests that the use of daily acyclovir (400 mg twice daily) may reduce the plasma viral load of HIV-1 and the risk of HIV-associated disease progression in individuals dually infected with HSV-2 and HIV-1.

Intravenous acyclovir is the treatment of choice for herpes simplex encephalitis, neonatal HSV infection, and serious HSV or VZV infections (Table 49–1). In immunocompromised patients with VZV infection, intravenous acyclovir reduces the incidence of cutaneous and visceral dissemination.

Topical acyclovir cream is substantially less effective than oral therapy for primary HSV infection. It is of no benefit in treating recurrent genital herpes.

Resistance to acyclovir can develop in HSV or VZV through alteration in either the viral thymidine kinase or the DNA polymerase, and clinically resistant infections have been reported in immunocompromised hosts. Most clinical isolates are resistant on the basis of deficient thymidine kinase activity and thus are cross-resistant to valacyclovir, famciclovir, and ganciclovir. Agents such as foscarnet, cidofovir, and trifluridine do not require activation by viral thymidine kinase and thus have preserved activity against the most prevalent acyclovir-resistant strains (Figure 49–3).

Acyclovir is generally well tolerated. Nausea, diarrhea, and headache have occasionally been reported. Intravenous infusion may be associated with reversible renal toxicity (ie, crystalline nephropathy or interstitial nephritis) or neurologic effects (eg, tremors, delirium, seizures). However, these are uncommon with adequate hydration and avoidance of rapid infusion rates. High doses of acyclovir cause chromosomal damage and testicular atrophy in rats, but there has been no evidence of teratogenicity, reduction in sperm production, or cytogenetic alterations in peripheral blood lymphocytes in patients receiving daily suppression of genital herpes for more than 10 years. A recent study found no evidence of increased birth defects in 1150 infants who were exposed to acyclovir during the first trimester.

Concurrent use of nephrotoxic agents may enhance the potential for nephrotoxicity. Probenecid and cimetidine decrease acyclovir clearance and increase exposure. Somnolence and lethargy may occur in patients receiving concomitant zidovudine and acyclovir.

VALACYCLOVIR

Valacyclovir is the L-valyl ester of acyclovir (Figure 49–2). It is rapidly converted to acyclovir after oral administration via first-pass enzymatic hydrolysis in the liver and intestine, resulting in serum levels that are three to five times greater than those achieved with oral acyclovir and approximate those achieved with intravenous acyclovir. Oral bioavailability is 54–70%, and cerebrospinal fluid levels are about 50% of those in serum. Elimination half-life is 2.5–3.3 hours.

Approved uses of valacyclovir include treatment of first or recurrent genital herpes, suppression of frequently recurring genital herpes, as a 1-day treatment for orolabial herpes, and as treatment for varicella and herpes zoster (Table 49–1). Once-daily dosing of valacyclovir for chronic suppression in persons with recurrent genital herpes has been shown to markedly decrease the risk of sexual transmission. In comparative trials with acyclovir for the treatment of patients with zoster, rates of cutaneous healing were similar, but valacyclovir was associated with a shorter duration of zoster-associated pain. Higher doses of valacyclovir (2 g four times daily) have also been shown to be effective in preventing CMV disease after organ transplantation when compared with placebo.

Valacyclovir is generally well tolerated, although nausea, headache, vomiting, or rash occasionally occur. At high doses, confusion, hallucinations, and seizures have been reported. AIDS patients who received high-dosage valacyclovir chronically (ie, 8 g/d) had an increased incidence of gastrointestinal intolerance as well as thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome; this dose has also been associated with confusion and hallucinations in transplant patients. In a recent study, there was no evidence of increased birth defects in 181 infants who were exposed to valacyclovir during the first trimester.

TABLE 49–1 Agents to treat or prevent herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections.

	Route of Administration	Use	Recommended Adult Dosage and Regimen
Acyclovir[1]	Oral	First episode genital herpes treatment	400 mg tid or 200 mg 5 times daily × 7–10 days
		Recurrent genital herpes treatment	400 mg tid or 200 mg 5 times daily or 800 mg bid × 3–5 days or 800 mg tid × 2 days
		Genital herpes in the HIV-infected host treatment	400 mg 3–5 times daily × 5–10 days
		Genital herpes suppression in the HIV-infected host	400–800 mg bid–tid
		Herpes proctitis treatment	400 mg 5 times daily until healed
		Orolabial herpes treatment	400 mg 5 times daily × 5 days
		Varicella treatment (age ≥ 2 years)	800 mg qid × 5 days
		Zoster treatment	800 mg 5 times daily × 7–10 days
	Intravenous	Severe HSV treatment	5 mg/kg q8h × 7–10 days
		Mucocutaneous herpes in the immunocompromised host treatment	10 mg/kg q8h × 7–14 days
		Herpes encephalitis treatment	10–15 mg/kg q8h × 14–21 days
		Neonatal HSV infection treatment	10–20 mg/kg q8h × 14–21 days
		Varicella or zoster in the immunosuppressed host treatment	10 mg/kg q8h × 7 days
	Topical (5% cream)	Herpes labialis treatment	Thin film covering lesion 5 times daily × 4 days
Famciclovir[1]	Oral	First episode genital herpes treatment	500 mg tid × 5–10 days
		Recurrent genital herpes treatment	1000 mg bid × 1 day
		Genital herpes in the HIV-infected host treatment	500 mg bid × 5–10 days
		Genital herpes suppression	250 mg bid
		Genital herpes suppression in the HIV-infected host	500 mg bid
		Orolabial herpes treatment	1500 mg once
		Orolabial or genital herpes suppression	250-500 mg bid
		Zoster	500 mg tid × 7 days
Valacyclovir[1]	Oral	First episode genital herpes treatment	1000 mg bid × 10 days
		Recurrent genital herpes treatment	500 mg bid × 3 days
		Genital herpes in the HIV-infected host treatment	500–1000 mg bid × 5–10 days
		Genital herpes suppression	500–1000 mg once daily
		Genital herpes suppression in the HIV-infected host	500 mg bid
		Orolabial herpes	2000 mg bid × 1 day
		Varicella (age ≥ 12 years)	20 mg/d tid × 5 days (maximum, 1 g tid)
		Zoster	1 g tid × 7 days
Foscarnet[1]	Intravenous	Acyclovir-resistant HSV and VZV infections	40 mg/kg q8h until healed
Docosanol	Topical (10% cream)	Recurrent herpes labialis	Thin film covering lesion q2h × 4 days
Penciclovir	Topical (1% cream)	Herpes labialis or herpes genitalis	Thin film covering lesions q2h × 4 days
Trifluridine	Topical (1% solution)	Acyclovir-resistant HSV infection	Thin film covering lesion 5 times daily until healed

[1]Dosage must be reduced in patients with renal insufficiency.

HSV, herpes simplex virus; VZV, varicella-zoster virus.

FAMCICLOVIR

Famciclovir is the diacetyl ester prodrug of 6-deoxypenciclovir, an acyclic guanosine analog (Figure 49–2). After oral administration, famciclovir is rapidly deacetylated and oxidized by first-pass metabolism to penciclovir. It is active in vitro against HSV-1, HSV-2, VZV, EBV, and HBV. As with acyclovir, activation by phosphorylation is catalyzed by the virus-specified thymidine kinase in infected cells, followed by competitive inhibition of the viral DNA polymerase to block DNA synthesis. Unlike acyclovir, however, penciclovir does not cause chain termination. Penciclovir triphosphate has lower affinity for the viral DNA polymerase than acyclovir triphosphate, but it achieves higher intracellular concentrations. The most commonly encountered clinical mutants of HSV are thymidine kinase-deficient; these are cross-resistant to acyclovir and famciclovir.

The bioavailability of penciclovir from orally administered famciclovir is 70%. The intracellular half-life of penciclovir triphosphate is prolonged, at 7–20 hours. Penciclovir is excreted primarily in the urine.

Oral famciclovir is effective for the treatment of first and recurrent genital herpes, for chronic daily suppression of genital herpes, for treatment of herpes labialis, and for the treatment of acute zoster (Table 49–1). One-day usage of famciclovir significantly accelerates time to healing of recurrent genital herpes and of herpes labialis. Comparison of famciclovir to valacyclovir for treatment of herpes zoster in immunocompetent patients showed similar rates of cutaneous healing and pain resolution; both agents shortened the duration of zoster-associated pain compared with acyclovir.

Oral famciclovir is generally well tolerated, although headache, nausea, or diarrhea may occur. As with acyclovir, testicular toxicity has been demonstrated in animals receiving repeated doses. However, men receiving daily famciclovir (250 mg every 12 hours) for 18 weeks had no changes in sperm morphology or motility. In a recent study, there was no evidence of increased birth defects in 32 infants who were exposed to famciclovir during the first trimester. The incidence of mammary adenocarcinoma was increased in female rats receiving famciclovir for 2 years.

PENCICLOVIR

The guanosine analog penciclovir, the active metabolite of famciclovir, is available for topical use. Penciclovir cream (1%) shortens the duration of recurrent herpes labialis or genitalis (Table 49–1). When applied within 1 hour of the onset of prodromal symptoms and continued every 2 hours during waking hours for 4 days, median time until healing was shortened by 17 hours compared with placebo. Adverse effects are uncommon, although application site reactions occur in about 1% of patients.

DOCOSANOL

Docosanol is a saturated 22-carbon aliphatic alcohol that inhibits fusion between the plasma membrane and the HSV envelope, thereby preventing viral entry into cells and subsequent viral replication. Topical docosanol 10% cream is available without a prescription; application site reactions occur in approximately 2% of patients. When applied within 12 hours of the onset of prodromal symptoms, five times daily, median healing time was shortened by 18 hours compared with placebo in recurrent orolabial herpes.

TRIFLURIDINE

Trifluridine (trifluorothymidine) is a fluorinated pyrimidine nucleoside that inhibits viral DNA synthesis in HSV-1, HSV-2, CMV, vaccinia, and some adenoviruses. It is phosphorylated intracellularly by host cell enzymes, and then competes with thymidine triphosphate for incorporation by the viral DNA polymerase (Figure 49–3). Incorporation of trifluridine triphosphate into both viral and host DNA prevents its systemic use. Application of a 1% solution is effective in treating keratoconjunctivitis and recurrent epithelial keratitis due to HSV-1 or HSV-2. Cutaneous application of trifluridine solution, alone or in combination with interferon alfa, has been used successfully in the treatment of acyclovir-resistant HSV infections.

INVESTIGATIONAL AGENTS

Valomaciclovir is an inhibitor of the viral DNA polymerase; it is currently under clinical evaluation for the treatment of patients with acute VZV infection (shingles) and acute EBV infection (infectious mononucleosis).

■ AGENTS TO TREAT CYTOMEGALOVIRUS (CMV) INFECTIONS

CMV infections occur primarily in the setting of advanced immunosuppression and are typically due to reactivation of latent infection. Dissemination of infection results in end-organ disease, including retinitis, colitis, esophagitis, central nervous system disease, and pneumonitis. Although the incidence in HIV-infected patients has markedly decreased with the advent of potent antiretroviral therapy, clinical reactivation of CMV infection after organ transplantation is still prevalent.

The availability of oral valganciclovir and the ganciclovir intraocular implant has decreased the use of intravenous ganciclovir, intravenous foscarnet, and intravenous cidofovir for the treatment of end-organ CMV disease (Table 49–2). Oral valganciclovir has largely replaced oral ganciclovir because of its lower pill burden.

GANCICLOVIR

Ganciclovir is an acyclic guanosine analog (Figure 49–2) that requires activation by triphosphorylation before inhibiting the viral DNA polymerase. Initial phosphorylation is catalyzed by the virus-specified protein kinase phosphotransferase UL97 in

TABLE 49–2 Agents to treat cytomegalovirus (CMV) infection.

Agent	Route of Administration	Use	Recommended Adult Dosage[1]
Valganciclovir	Oral	CMV retinitis treatment	Induction: 900 mg bid × 21 days
			Maintenance: 900 mg daily
	Oral	CMV prophylaxis (transplant patients)	900 mg daily
Ganciclovir	Intravenous	CMV retinitis treatment	Induction: 5 mg/kg q12h × 14–21 days
			Maintenance: 5 mg/kg/d or 6 mg/kg five times per week
	Oral	CMV prophylaxis	1 g tid
		CMV retinitis treatment	1 g tid
	Intraocular implant	CMV retinitis treatment	4.5 mg every 5–8 months
Foscarnet	Intravenous	CMV retinitis treatment	Induction: 60 mg/kg q8h or 90 mg/kg q12h × 14–21 days
			Maintenance: 90–120 mg/kg/d
Cidofovir	Intravenous	CMV retinitis treatment	Induction: 5 mg/kg/wk × 2 weeks Maintenance: 5 mg/kg every week

[1]Dosage must be reduced in patients with renal insufficiency.

CMV-infected cells. The activated compound competitively inhibits viral DNA polymerase and causes termination of viral DNA elongation (Figure 49–3). Ganciclovir has in vitro activity against CMV, HSV, VZV, EBV, HHV-6, and HHV-8. Its activity against CMV is up to 100 times greater than that of acyclovir.

Ganciclovir may be administered intravenously, orally, or via intraocular implant. The bioavailability of oral ganciclovir is poor. Cerebrospinal fluid concentrations are approximately 50% of serum concentrations. The elimination half-life is 4 hours, and the intracellular half-life is prolonged at 16–24 hours. Clearance of the drug is linearly related to creatinine clearance. Ganciclovir is readily cleared by hemodialysis.

Intravenous ganciclovir has been shown to delay progression of CMV retinitis in patients with AIDS. Dual therapy with foscarnet and ganciclovir is more effective in delaying progression of retinitis than either drug alone (see Foscarnet), although adverse effects are compounded. Intravenous ganciclovir is also used to treat CMV colitis, esophagitis, and pneumonitis (the latter often treated with a combination of ganciclovir and intravenous cytomegalovirus immunoglobulin) in immunocompromised patients. Intravenous ganciclovir, followed by either oral ganciclovir or high-dose oral acyclovir, reduces the risk of CMV infection in transplant recipients. Oral ganciclovir is indicated for prevention of end-organ CMV disease in AIDS patients and as maintenance therapy of CMV retinitis after induction. Although less effective than intravenous ganciclovir, the oral form carries a diminished risk of myelosuppression and of catheter-related complications. The risk of Kaposi's sarcoma is reduced in AIDS patients receiving long-term ganciclovir, presumably because of activity against HHV-8.

Ganciclovir may also be administered intraocularly to treat CMV retinitis, either by direct intravitreal injection or by intraocular implant. The implant has been shown to delay progression of retinitis to a greater degree than systemic ganciclovir therapy. Surgical replacement of the implant is required at intervals of 5–8 months. Concurrent therapy with a systemic anti-CMV agent is recommended to prevent other sites of end-organ CMV disease.

Resistance to ganciclovir increases with duration of usage. The more common mutation, in UL97, results in decreased levels of the triphosphorylated (ie, active) form of ganciclovir. The less common UL54 mutation in DNA polymerase results in higher levels of resistance and potential cross-resistance with cidofovir and foscarnet. Antiviral susceptibility testing is recommended in patients in whom resistance is suspected clinically, as is the substitution of alternative therapies and concomitant reduction in immunosuppressive therapies, if possible. The addition of CMV hyperimmune globulin may also be considered.

The most common adverse effect of systemic ganciclovir treatment, particularly after intravenous administration, is myelosuppression. Myelosuppression may be additive in patients receiving concurrent zidovudine, azathioprine, or mycophenolate mofetil. Other potential adverse effects are nausea, diarrhea, fever, rash, headache, insomnia, and peripheral neuropathy. Central nervous system toxicity (confusion, seizures, psychiatric disturbance) and hepatotoxicity have been rarely reported. Ganciclovir is mutagenic in mammalian cells and carcinogenic and embryotoxic at high doses in animals and causes aspermatogenesis; the clinical significance of these preclinical data is unclear.

Levels of ganciclovir may rise in patients concurrently taking probenecid or trimethoprim. Concurrent use of ganciclovir with didanosine may result in increased levels of didanosine.

VALGANCICLOVIR

Valganciclovir is an L-valyl ester prodrug of ganciclovir that exists as a mixture of two diastereomers (Figure 49–2). After oral administration, both diastereomers are rapidly hydrolyzed to ganciclovir by esterases in the intestinal wall and liver.

Valganciclovir is well absorbed and rapidly metabolized in the intestinal wall and liver to ganciclovir; no other metabolites have been detected. The bioavailability of oral valganciclovir is 60%; it is recommended that the drug be taken with food. The AUC_{0-24h} resulting from valganciclovir (900 mg once daily) is similar to that after 5 mg/kg once daily of intravenous ganciclovir and approximately 1.65 times that of oral ganciclovir. The major route of elimination is renal, through glomerular filtration and active tubular secretion. Plasma concentrations of valganciclovir are reduced approximately 50% by hemodialysis.

Valganciclovir is indicated for the treatment of CMV retinitis in patients with AIDS and for the prevention of CMV disease in high-risk kidney, heart, and kidney-pancreas transplant patients. Adverse effects, drug interactions, and resistance patterns are the same as those associated with ganciclovir.

FOSCARNET

Foscarnet (phosphonoformic acid) is an inorganic pyrophosphate analog (Figure 49–2) that inhibits herpesvirus DNA polymerase, RNA polymerase, and HIV reverse transcriptase directly without requiring activation by phosphorylation. Foscarnet blocks the pyrophosphate binding site of these enzymes and inhibits cleavage of pyrophosphate from deoxynucleotide triphosphates. It has in vitro activity against HSV, VZV, CMV, EBV, HHV-6, HHV-8, HIV-1, and HIV-2.

Foscarnet is available in an intravenous formulation only; poor oral bioavailability and gastrointestinal intolerance preclude oral use. Cerebrospinal fluid concentrations are 43–67% of steady-state serum concentrations. Although the mean plasma half-life is 3–7 hours, up to 30% of foscarnet may be deposited in bone, with a half-life of several months. The clinical repercussions of this are unknown. Clearance of foscarnet is primarily renal and is directly proportional to creatinine clearance. Serum drug concentrations are reduced approximately 50% by hemodialysis.

Foscarnet is effective in the treatment of CMV retinitis, CMV colitis, CMV esophagitis, acyclovir-resistant HSV infection, and acyclovir-resistant VZV infection. The dosage of foscarnet must be titrated according to the patient's calculated creatinine clearance before each infusion. Use of an infusion pump to control the rate of infusion is important to prevent toxicity, and large volumes of fluid are required because of the drug's poor solubility. The combination of ganciclovir and foscarnet is synergistic in vitro against CMV and has been shown to be superior to either agent alone in delaying progression of retinitis; however, toxicity is also increased when these agents are administered concurrently. As with ganciclovir, a decrease in the incidence of Kaposi's sarcoma has been observed in patients who have received long-term foscarnet.

Foscarnet has been administered intravitreally for the treatment of CMV retinitis in patients with AIDS, but data regarding efficacy and safety are incomplete.

Resistance to foscarnet in HSV and CMV isolates is due to point mutations in the DNA polymerase gene and is typically associated with prolonged or repeated exposure to the drug. Mutations in the HIV-1 reverse transcriptase gene have also been described. Although foscarnet-resistant CMV isolates are typically cross-resistant to ganciclovir, foscarnet activity is usually maintained against ganciclovir- and cidofovir-resistant isolates of CMV.

Potential adverse effects of foscarnet include renal impairment, hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, and hypomagnesemia. Saline preloading helps prevent nephrotoxicity, as does avoidance of concomitant administration of drugs with nephrotoxic potential (eg, amphotericin B, pentamidine, aminoglycosides). The risk of severe hypocalcemia, caused by chelation of divalent cations, is increased with concomitant use of pentamidine. Genital ulcerations associated with foscarnet therapy may be due to high levels of ionized drug in the urine. Nausea, vomiting, anemia, elevation of liver enzymes, and fatigue have been reported; the risk of anemia may be additive in patients receiving concurrent zidovudine. Central nervous system toxicity includes headache, hallucinations, and seizures; the risk of seizures may be increased with concurrent use of imipenem. Foscarnet caused chromosomal damage in preclinical studies.

CIDOFOVIR

Cidofovir (Figure 49–2) is a cytosine nucleotide analog with in vitro activity against CMV, HSV-1, HSV-2, VZV, EBV, HHV-6, HHV-8, adenovirus, poxviruses, polyomaviruses, and human papillomavirus. In contrast to ganciclovir, phosphorylation of cidofovir to the active diphosphate is independent of viral enzymes (Figure 49–3); thus activity is maintained against thymidine kinase-deficient or -altered strains of CMV or HSV. Cidofovir diphosphate acts both as a potent inhibitor of and as an alternative substrate for viral DNA polymerase, competitively inhibiting DNA synthesis and becoming incorporated into the viral DNA chain. Cidofovir-resistant isolates tend to be cross-resistant with ganciclovir but retain susceptibility to foscarnet.

Although the terminal half-life of cidofovir is approximately 2.6 hours, the active metabolite cidofovir diphosphate, has a prolonged intracellular half-life of 17–65 hours, thus allowing infrequent dosing. A separate metabolite, cidofovir phosphocholine, has a half-life of at least 87 hours and may serve as an intracellular reservoir of active drug. Cerebrospinal fluid penetration is poor. Elimination is by active renal tubular secretion. High-flux hemodialysis reduces serum levels of cidofovir by approximately 75%.

Intravenous cidofovir is effective for the treatment of CMV retinitis and is used experimentally to treat adenovirus, human papillomavirus, and poxvirus infections. Intravenous cidofovir must be administered with high-dose probenecid (2 g at 3 hours before the infusion and 1 g at 2 and 8 hours after), which blocks active tubular secretion and decreases nephrotoxicity. Before each infusion, cidofovir dosage must be adjusted for alterations in the calculated creatinine clearance or for the presence of urine protein, and aggressive adjunctive hydration is required. Initiation of cidofovir therapy is contraindicated in patients with existing renal insufficiency. Direct intravitreal administration of cidofovir is not recommended because of ocular toxicity.

The primary adverse effect of intravenous cidofovir is a dose-dependent proximal tubular nephrotoxicity, which may be reduced with prehydration using normal saline. Proteinuria, azotemia, metabolic acidosis, and Fanconi's syndrome may occur. Concurrent administration of other potentially nephrotoxic agents (eg, amphotericin B, aminoglycosides, nonsteroidal anti-inflammatory drugs, pentamidine, foscarnet) should be avoided. Prior administration of foscarnet may increase the risk of nephrotoxicity. Other potential adverse effects include uveitis, ocular hypotony, and neutropenia (15–24%). Concurrent probenecid use may result in other toxicities or drug-drug interactions (see Chapter 36). Cidofovir is mutagenic, gonadotoxic, and embryotoxic, and caused mammary adenocarcinomas in rats.

ANTIRETROVIRAL AGENTS

Substantial advances have been made in antiretroviral therapy since the introduction of the first agent, zidovudine, in 1987 (Table 49–3). Greater knowledge of viral dynamics through the use of viral load and resistance testing has made it clear that combination therapy with maximally potent agents will reduce viral replication to the lowest possible level and decrease the likelihood of emergence of resistance. Thus, administration of combination antiretroviral therapy, typically comprising at least three antiretroviral agents, has become the standard of care. Viral susceptibility to specific agents varies among patients and may change with time, owing to development of resistance. Therefore, such combinations must be chosen with care and tailored to the individual, as must changes to a given regimen. In addition to potency and susceptibility, important factors in the selection of agents for any given patient are tolerability, convenience, and optimization of adherence.

The retroviral genomic RNA serves as the template for synthesis of a double-stranded DNA copy, the provirus (Figure 49–4). Synthesis of the provirus is mediated by a virus-encoded RNA-dependent DNA polymerase, or "reverse transcriptase." The provirus is translocated to the nucleus and integrated into host DNA. Transcription of this integrated DNA is regulated primarily by cellular machinery.

Six classes of antiretroviral agents are currently available for use: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 receptor antagonists, and integrase inhibitors. As new agents have become available, several older ones have had diminished usage, because of either suboptimal safety profile or inferior antiviral potency. It is important to recognize that the high rate of mutation of HIV-1 per replication cycle results in a great potential for genotypic variation. Genotypic resistance has been reported for each of the antiretroviral agents currently in use. Treatment that slows or stops replication is critical in reducing the number of cumulative mutations, as is the use of combinations of agents with differing susceptibility patterns.

Discussion of antiretroviral agents in this chapter is specific to HIV-1. It should be noted that in vitro susceptibility of HIV-2 to the NRTIs is similar to that of HIV-1, albeit with a lower genetic barrier to resistance. There is innate resistance of HIV-2 to the NNRTIs, due to a different structure of the reverse transcriptases' NNRTI binding pockets; enfuvirtide (see below) has no activity against HIV-2. Data on the activity of PI agents and maraviroc against HIV-2 are sparse and inconclusive.

NUCLEOSIDE & NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

The NRTIs act by competitive inhibition of HIV-1 reverse transcriptase; incorporation into the growing viral DNA chain causes premature chain termination due to inhibition of binding with the incoming nucleotide (Figure 49–4). Each agent requires intracytoplasmic activation via phosphorylation by cellular enzymes to the triphosphate form.

Typical resistance mutations include M184V, L74V, D67N, and M41L. Lamivudine or emtricitabine therapy tends to select rapidly for the M184V mutation in regimens that are not fully suppressive. While the M184V mutation confers reduced susceptibility to abacavir, didanosine, and zalcitabine, its presence may restore phenotypic susceptibility to zidovudine. The K65R mutation is associated with reduced susceptibility to tenofovir, abacavir, lamivudine, and emtricitabine.

All NRTIs may be associated with mitochondrial toxicity, probably owing to inhibition of mitochondrial DNA polymerase gamma. Less commonly, lactic acidosis with hepatic steatosis may occur, which can be fatal. NRTI treatment should be suspended in the setting of rapidly rising aminotransferase levels, progressive hepatomegaly, or metabolic acidosis of unknown cause. The thymidine analogs zidovudine and stavudine may be particularly associated with dyslipidemia and insulin resistance. Also, some evidence suggests an increased risk of myocardial infarction in patients receiving abacavir or didanosine; this bears further investigation.

ABACAVIR

Abacavir is a guanosine analog (Figure 49–2) that is well absorbed following oral administration (83%) and is unaffected by food. The serum half-life is 1.5 hours. The drug undergoes hepatic glucuronidation and carboxylation. Cerebrospinal fluid levels are approximately one third those of plasma.

Abacavir is often co-administered with lamivudine, and a once-daily, fixed-dose combination formulation is available. Abacavir is also available in a fixed-dose combination with lamivudine and zidovudine.

High-level resistance to abacavir appears to require at least two or three concomitant mutations and thus tends to develop slowly.

Hypersensitivity reactions, occasionally fatal, have been reported in up to 8% of patients receiving abacavir and may be more severe in association with once-daily dosing. Symptoms, which generally occur within the first 6 weeks of therapy, include fever, fatigue, nausea, vomiting, diarrhea, and abdominal pain.

TABLE 49–3 Currently available antiretroviral agents.

Agent	Class of Agent	Recommended Adult Dosage	Administration Recommendation	Characteristic Adverse Effects	Comments
Abacavir	NRTI[1]	300 mg bid or 600 mg qd	Testing to rule out the presence of the HLA-B5701 allele is recommended prior to the initiation of therapy	Rash, hypersensitivity reaction, nausea. Possible increase in myocardial infarction	Avoid alcohol
Atazanavir	PI[2]	400 mg qd or 300 mg qd with ritonavir 100 mg qd. Adjust dose in hepatic insufficiency	Take with food. Separate dosing from ddI or antacids by 1 h. Separate dosing from cimetidine and other acid-reducing agents by 12 h	Nausea, vomiting, diarrhea, abdominal pain, headache, peripheral neuropathy, skin rash, indirect hyperbilirubinemia, prolonged PR and/or QT_c interval	See footnote 4 for contraindicated medications. Also avoid etravirine, fosamprenavir, nevirapine, and proton pump inhibitors. Avoid in severe hepatic insufficiency
Darunavir	PI[2]	Treatment- experienced: 600 mg bid with ritonavir 100 mg bid. Treatment-naïve: 800 mg qd with ritonavir 100 mg qd. Tablets can be dissolved in water	Take with food	Diarrhea, headache, nausea, rash, hyperlipidemia, ↑ liver enzymes, ↑ serum amylase	Avoid in patients with sulfa allergy. See footnote 4 for contraindicated medications
Delavirdine	NNRTI	400 mg tid	Separate dosing from ddI or antacids by 1 h	Rash, ↑ liver enzymes, headache, nausea, diarrhea	See footnote 4 for contraindicated medications. Also avoid concurrent fosamprenavir and rifabutin. Teratogenic in rats
Didanosine (ddI)	NRTI[1]	Tablets, 400 mg qd or 200 mg bid,[3] adjusted for weight. Buffered powder, 250 mg bid[3]	30 min before or 2 h after meals. Separate dosing from fluoroquinolones and tetracyclines by 2 h	Peripheral neuropathy, pancreatitis, diarrhea, nausea, hyperuricemia. Possible increase in myocardial infarction	Avoid concurrent neuropathic drugs (eg, stavudine, zalcitabine, isoniazid), ribavirin, and alcohol. Do not administer with tenofovir
Efavirenz	NNRTI	600 mg qd	Take on an empty stomach. Bedtime dosing recommended initially to minimize central nervous system side effects	Central nervous system effects, rash, ↑ liver enzymes, headache, nausea	See footnote 4 for contraindicated medications. Teratogenic in primates
Emtricitabine	NRTI[1]	200 mg qd.[3] Tablets can be dissolved in water	Oral solution should be refrigerated	Headache, diarrhea, nausea, asthenia, skin hyperpigmentation	Do not administer concurrent lamivudine. Avoid disulfiram and metronidazole with oral solution
Enfuvirtide	Fusion inhibitor	90 mg subcutaneously bid	Store at room temperature as a powder; refrigerate once reconstituted	Local injection site reactions, hypersensitivity reaction	
Etravirine	NNRTI	200 mg bid	Take after a meal; do not take on an empty stomach	Rash, nausea, diarrhea	See footnote 4 for contraindicated medications. Do not administer with other NNRTIs, indinavir, atazanavir-ritonavir, fosamprenavir-ritonavir, tipranavir-ritonavir, or any unboosted PI
Fosamprenavir	PI[2]	1400 mg bid or 700 mg bid with ritonavir 100 mg bid or 1400 mg daily with ritonavir 100–200 mg qd. Adjust dose in hepatic insufficiency	Separate dosing from antacids or didanosine by ≥ 1 h. Avoid concurrent high-fat meals	Diarrhea, nausea, vomiting, hypertriglyceridemia, rash, headache, perioral paresthesias, ↑ liver enzymes	See footnote 4 for contraindicated medications. Do not administer with etravirine; do not administer with lopinavir/ritonavir or in severe hepatic insufficiency. Also avoid cimetidine, disulfiram, metronidazole, vitamin E, ritonavir oral solution, and alcohol when using the oral solution

(*continued*)

TABLE 49–3 Currently available antiretroviral agents. (Continued)

Agent	Class of Agent	Recommended Adult Dosage	Administration Recommendation	Characteristic Adverse Effects	Comments
Indinavir	PI[2]	800 mg tid or 800 mg bid with ritonavir 100–200 mg bid. Adjust dose in hepatic insufficiency	Best on an empty stomach. Drink at least 48 oz liquid daily. Separate dosing from ddI by 1 h. Store in original container, which contains desiccant	Nephrolithiasis, nausea, indirect hyperbilirubinemia, headache, asthenia, blurred vision	See footnote 4 for contraindicated medications. Do not administer with etravirine
Lamivudine	NRTI[1]	150 mg bid or 300 mg qd[3]		Nausea, headache, dizziness, fatigue	Do not administer with zalcitabine
Lopinavir/ritonavir	PI/PI[2]	Treatment-experienced: 400 mg/100 mg bid. Treatment-naïve: 800 mg/200 mg qd. May need dose adjustment in hepatic insufficiency	Take with food. Separate dosing from ddI by 1 h. Store capsules and solution in refrigerator	Diarrhea, abdominal pain, nausea, hypertriglyceridemia, headache, ↑ liver enzymes	See footnote 4 for contraindicated medications. Also avoid fosamprenavir. Avoid disulfiram and metronidazole with oral solution
Maraviroc	CCR5 inhibitor	300 mg bid; 150 bid with CYP3A inhibitors; 600 mg bid with CYP3A inducers[3]		Muscle and joint pain, diarrhea, sleep disturbance, ↑ liver enzymes	See footnote 4 for medications that must be co-administered with caution. Avoid rifampin
Nelfinavir	PI[2]	750 mg tid or 1250 mg bid	Take with food	Diarrhea, nausea, flatulence	See footnote 4 for contraindicated medications. Do not administer with etravirine
Nevirapine	NNRTI	200 mg bid. Adjust dose in hepatic insufficiency	Dose-escalate from 200 mg daily over 14 days to decrease frequency of rash	Rash, hepatitis (occasionally fulminant), nausea, headache	See footnote 4 for contraindicated medications. Do not administer with atazanavir
Raltegravir	Integrase inhibitor	400 mg bid. Increase dose to 800 mg bid if administered with rifampin	Separate dosing from antacids by ≥ 4 h	Diarrhea, nausea, fatigue, headache, dizziness, muscle aches, ↑ creatine kinase	Avoid rifampin
Ritonavir	PI[2]	600 mg bid	Take with food. Separate dosing with ddI by 2 h. Dose-escalate from 300 mg bid over 1–2 weeks to improve tolerance. Refrigerate capsules but not oral solution	Nausea, diarrhea, paresthesias, hepatitis	See footnote 4 for contraindicated medications. Avoid disulfiram and metronidazole with oral solution
Saquinavir	PI[2]	1000 mg bid with ritonavir 100 mg bid	Take within 2 h of a full meal. Refrigeration recommended	Nausea, diarrhea, rhinitis, abdominal pain, dyspepsia, rash	See footnote 4 for contraindicated medications. Avoid in severe hepatic insufficiency. Use sunscreen owing to an increase in photosensitivity. Avoid concomitant garlic capsules
Stavudine	NRTI[1]	30–40 mg bid, depending on weight[3]		Peripheral neuropathy, lipodystrophy, hyperlipidemia, rapidly progressive ascending neuromuscular weakness (rare), pancreatitis	Avoid concurrent zidovudine and neuropathic drugs (eg, ddI, zalcitabine, isoniazid)
Tenofovir	NRTI[1]	300 mg qd[3]	Take with food	Nausea, diarrhea, vomiting, flatulence, headache, renal insufficiency	Avoid concurrent atazanavir, probenecid, didanosine
Tipranavir	PI[2]	500 mg bid with ritonavir 200 mg bid. Avoid use in hepatic insufficiency	Take with food. Separate from ddI by at least 2 h. Avoid antacids. Avoid in patients with sulfa allergy. Refrigeration required	Diarrhea, nausea, vomiting, abdominal pain, rash, ↑ liver enzymes, hypercholesterolemia, hypertriglyceridemia	See footnote 4 for contraindicated medications. Avoid concurrent fosamprenavir, saquinavir, etravirine. Do not administer to patients at risk for bleeding

(*continued*)

TABLE 49–3 Currently available antiretroviral agents. (Continued)

Agent	Class of Agent	Recommended Adult Dosage	Administration Recommendation	Characteristic Adverse Effects	Comments
Zalcitabine	NRTI[1]	0.75 mg tid[3]	Administer 1 h before or 2 h after an antacid	Peripheral neuropathy; oral ulcerations, pancreatitis, headache, nausea, rash, arthralgias	Avoid concurrent cimetidine; avoid concurrent neuropathic drugs (eg, ddI, stavudine, isoniazid). Do not administer with lamivudine
Zidovudine	NRTI[1]	200 mg tid or 300 mg bid[3]		Macrocytic anemia, neutropenia, nausea, headache, insomnia, asthenia	Avoid concurrent stavudine and myelosuppressive drugs (eg, ganciclovir, ribavirin)

[1]All NRTI agents, including tenofovir, carry the risk of lactic acidosis with hepatic steatosis as a potential adverse event.

[2]All PI agents, with the possible exception of fosamprenavir, carry the risk of hyperlipidemia, fat maldistribution, hyperglycemia, and insulin resistance as potential adverse events.

[3]Adjust dose in renal insufficiency.

[4]Because of altered systemic exposures, contraindicated concurrent drugs generally include antiarrhythmics (flecainide, propafenone), antihistamines (astemizole, terfenadine), sedative-hypnotics (alprazolam, diazepam, flurazepam, midazolam, triazolam, trazodone, clorazepate), neuroleptics (pimozide), ergot alkaloid derivatives, HMG-CoA reductase inhibitors (atorvastatin, simvastatin, lovastatin, rosuvastatin), anticonvulsants (phenobarbital, phenytoin), oral contraceptives (ethinyl estradiol/norethindrone acetate), cisapride, rifampin, rifapentine, and St. John's wort. Drugs that should be used with caution owing to altered levels include amiodarone, bepridil, quinidine, lidocaine, nifedipine, nicardipine, felodipine, sildenafil, vardenafil, tadalafil, warfarin, levodopa, tacrolimus, cyclosporine, rapamycin, voriconazole, itraconazole, ketoconazole, carbamazepine, desipramine, bupropion, dofetilide, fluticasone, atovaquone, dapsone, dexamethasone, methadone, omeprazole, and lansoprazole. The dosages of rifabutin and clarithromycin should be decreased when administered concurrently.

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

Respiratory symptoms such as dyspnea, pharyngitis, and cough may also be present, and skin rash occurs in about 50% of patients. The laboratory abnormalities of a mildly elevated serum aminotransferase or creatine kinase level may be present but are nonspecific. Although the syndrome tends to resolve quickly with discontinuation of medication, rechallenge with abacavir results in return of symptoms within hours and may be fatal. Testing for the HLA-B5701 allele before initiation of abacavir therapy is recommended to identify patients with an increased risk for an abacavir-associated hypersensitivity reaction. Although the positive predictive value of this test is only about 50%, it has a negative predictive value of approximately 100%.

Other potential adverse events are rash, fever, nausea, vomiting, diarrhea, headache, dyspnea, fatigue, and pancreatitis (rare). Abacavir should be used cautiously in patients with existing cardiac risk factors due to a possible increased risk of myocardial events. Since abacavir may lower methadone levels, patients receiving these two agents concurrently should be monitored for signs of opioid withdrawal and may require an increased dose of methadone.

DIDANOSINE

Didanosine (ddI) is a synthetic analog of deoxyadenosine (Figure 49–2). Oral bioavailability is approximately 40%; dosing on an empty stomach is optimal, but buffered formulations are necessary to prevent inactivation by gastric acid (Table 49–3). Cerebrospinal fluid concentrations of the drug are approximately 20% of serum concentrations. Serum half-life is 1.5 hours, but the intracellular half-life of the activated compound is as long as 20–24 hours. The drug is eliminated by both cellular metabolism and renal excretion.

The major clinical toxicity associated with didanosine therapy is dose-dependent pancreatitis. Other risk factors for pancreatitis (eg, alcohol abuse, hypertriglyceridemia) are relative contraindications, and concurrent drugs with the potential to cause pancreatitis, including zalcitabine, stavudine, ribavirin, and hydroxyurea, should be avoided (Table 49–3). The risk of peripheral distal sensory neuropathy, another potential toxicity, may be increased with concurrent use of stavudine, isoniazid, vincristine, or ribavirin. Other reported adverse effects include diarrhea (particularly with the buffered formulation), hepatitis, esophageal ulceration, cardiomyopathy, central nervous system toxicity (headache, irritability, insomnia), and hypertriglyceridemia. Previously asymptomatic hyperuricemia may precipitate attacks of gout in susceptible individuals; concurrent use of allopurinol may increase levels of didanosine. Reports of retinal changes and optic neuritis in patients receiving didanosine, particularly in adults receiving high doses and in children, mandate periodic retinal examinations. Lipoatrophy appears to be more common in patients receiving didanosine or other thymidine analogs. As with abacavir, didanosine should be used cautiously in patients with cardiac risk factors due to a possibly increased risk of myocardial infarction.

The buffer in didanosine tablets and powder interferes with absorption of indinavir, delavirdine, atazanavir, dapsone, itraconazole, and fluoroquinolone agents; therefore, administration should be separated in time. Serum levels of didanosine are increased when co-administered with tenofovir or ganciclovir, and are decreased by atazanavir, delavirdine, ritonavir, tipranavir, and methadone (Table 49–4).

EMTRICITABINE

Emtricitabine (FTC) is a fluorinated analog of lamivudine with a long intracellular half-life (> 24 hours), allowing for once-daily dosing (Figure 49–2). Oral bioavailability of the capsules is 93% and is unaffected by food, but penetration into the cerebrospinal

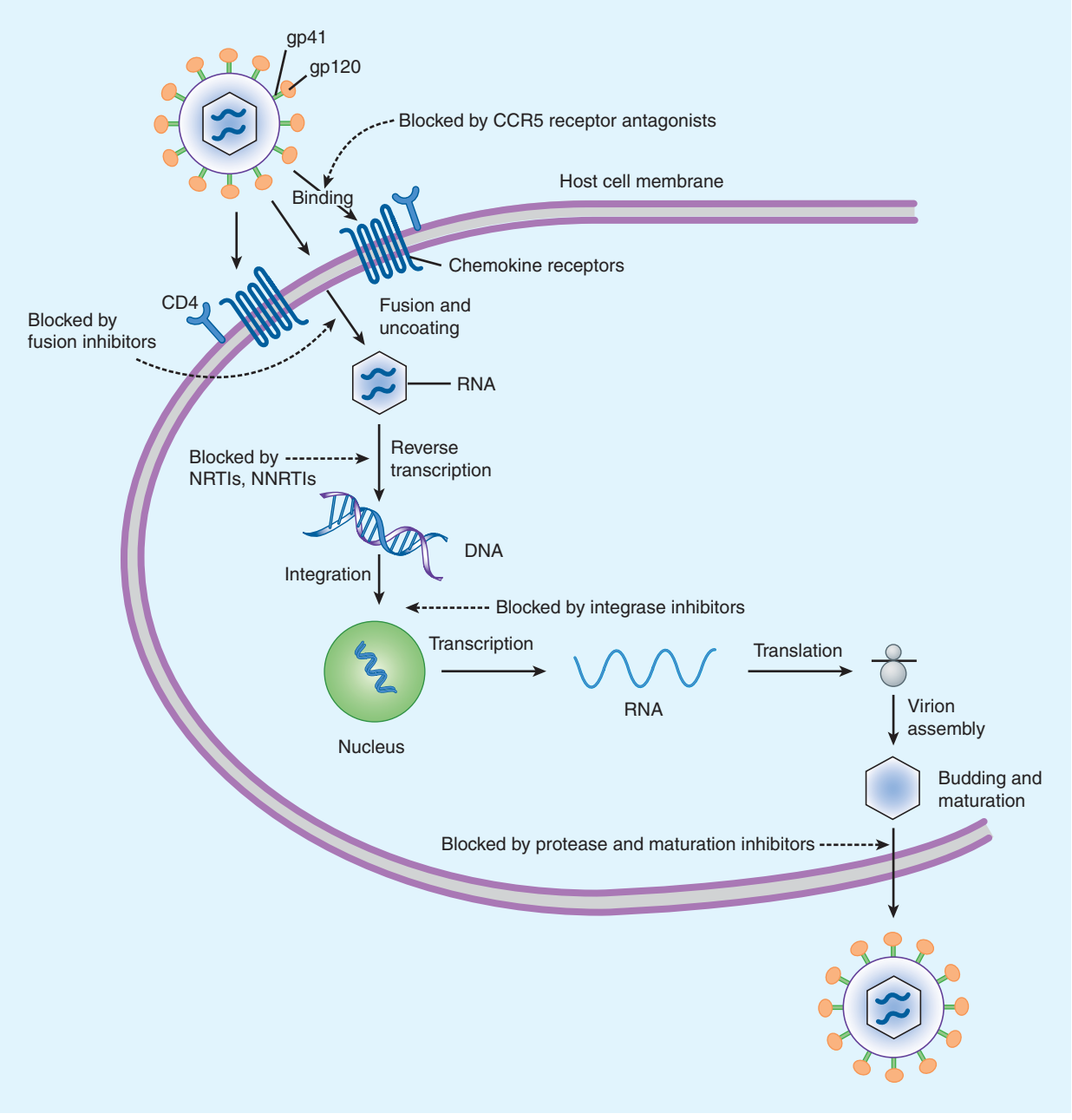

FIGURE 49–4 Life cycle of HIV. Binding of viral glycoproteins to host cell CD4 and chemokine receptors leads to fusion of the viral and host cell membranes via gp41 and entry of the virion into the cell. After uncoating, reverse transcription copies the single-stranded HIV RNA genome into double-stranded DNA, which is integrated into the host cell genome. Gene transcription by host cell enzymes produces messenger RNA, which is translated into proteins that assemble into immature noninfectious virions that bud from the host cell membrane. Maturation into fully infectious virions is through proteolytic cleavage. NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors.

fluid is low. Elimination is by both glomerular filtration and active tubular secretion. The serum half-life is about 10 hours.

The oral solution, which contains propylene glycol, is contraindicated in young children, pregnant women, patients with renal or hepatic failure, and those using metronidazole or disulfiram. Also, because of its activity against HBV, patients co-infected with HIV and HBV should be closely monitored if treatment with emtricitabine is interrupted or discontinued, owing to the likelihood of hepatitis flare.

Emtricitabine is often co-administered with tenofovir, and a once-daily, fixed-dose combination formulation is available, both alone and in combination with efavirenz. In a recent placebo-controlled study, use of emtricitabine and tenofovir was effective as preexposure prophylaxis, reducing HIV acquisition in men who have sex with men.

Like lamivudine, the M184V/I mutation is most frequently associated with emtricitabine use and may emerge rapidly in

TABLE 49–4 Clinically significant drug-drug interactions pertaining to two-drug antiretroviral combinations.[1]

Agent	Drugs That Increase Its Serum Levels	Drugs That Decrease Its Serum Levels
Abacavir		Tipranavir
Atazanavir	Ritonavir	Didanosine, efavirenz, etravirine, nevirapine, ritonavir, stavudine, tenofovir, tipranavir
Darunavir	Indinavir	Lopinavir/ritonavir, saquinavir
Delavirdine	Etravirine	Didanosine, fosamprenavir, lopinavir, nelfinavir, ritonavir
Didanosine	Tenofovir	Atazanavir, delavirdine, ritonavir, tipranavir
Efavirenz	Darunavir	Etravirine, nelfinavir, nevirapine
Etravirine	Delavirdine	Darunavir, efavirenz, nevirapine, ritonavir, saquinavir, tipranavir
Fosamprenavir	Atazanavir, delavirdine, etravirine, indinavir, nelfinavir	Efavirenz, lopinavir/ritonavir, nevirapine, tipranavir
Indinavir	Darunavir, delavirdine, nelfinavir, tipranavir, zidovudine	Didanosine, fosamprenavir, efavirenz, etravirine, nevirapine
Lopinavir/ritonavir	Darunavir, delavirdine, indinavir, ritonavir	Efavirenz, nelfinavir, nevirapine, tenofovir, tipranavir
Maraviroc	Atazanavir, darunavir, delavirdine, lopinavir/ritonavir, nevirapine	Efavirenz, etravirine
Nelfinavir	Delavirdine, etravirine, indinavir, ritonavir	Nevirapine
Nevirapine	Atazanavir, fosamprenavir, lopinavir	Etravirine
Ritonavir	Delavirdine	Tenofovir
Saquinavir	Atazanavir, delavirdine, indinavir, lopinavir, nelfinavir, ritonavir	Efavirenz, etravirine, nevirapine, tipranavir
Tenofovir	Atazanavir, lopinavir/ritonavir	
Tipranavir	Enfuvirtide	Efavirenz

[1]Dose adjustment may be necessary if co-administered.

patients receiving regimens that are not fully suppressive. Because of their similar mechanisms of action and resistance profiles, the combination of lamivudine and emtricitabine is not recommended.

The most common adverse effects observed in patients receiving emtricitabine are headache, diarrhea, nausea, and rash. In addition, hyperpigmentation of the palms or soles may be observed (~ 3%), particularly in African-Americans (up to 13%). No drug-drug interactions of note have been reported to date.

LAMIVUDINE

Lamivudine (3TC) is a cytosine analog (Figure 49–2) with in vitro activity against HIV-1 that is synergistic with a variety of antiretroviral nucleoside analogs—including zidovudine and stavudine—against both zidovudine-sensitive and zidovudine-resistant HIV-1 strains. As with emtricitabine, lamivudine has activity against HBV; therefore, discontinuation in patients that are co-infected with HIV and HBV may be associated with a flare of hepatitis.

Oral bioavailability exceeds 80% and is not food-dependent. In children, the average cerebrospinal fluid:plasma ratio of lamivudine was 0.2. Serum half-life is 2.5 hours, whereas the intracellular half-life of the triphosphorylated compound is 11–14 hours. Most of the drug is eliminated unchanged in the urine.

Lamivudine is often co-administered with abacavir, and a once-daily, fixed-dose combination formulation is available. Lamivudine is also available in a fixed-dose combination with zidovudine, either alone or in combination with abacavir.

Lamivudine therapy rapidly selects for the M184V mutation in regimens that are not fully suppressive.

Potential adverse effects are headache, dizziness, insomnia, fatigue, dry mouth, and gastrointestinal discomfort, although these are typically mild and infrequent. Lamivudine's bioavailability increases when it is co-administered with trimethoprim-sulfamethoxazole. Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another; therefore, their concurrent use should be avoided if possible. Short-term safety of lamivudine has been demonstrated for both mother and infant.

STAVUDINE

The thymidine analog stavudine (d4T) (Figure 49–2) has high oral bioavailability (86%) that is not food-dependent. The serum half-life is 1.1 hours, the intracellular half-life is 3.0–3.5 hours, and mean cerebrospinal fluid concentrations are 55% of those of plasma. Excretion is by active tubular secretion and glomerular filtration.

The major toxicity is a dose-related peripheral sensory neuropathy. The incidence of neuropathy may be increased when stavudine is administered with other neuropathy-inducing drugs such as didanosine, zalcitabine, vincristine, isoniazid, or ribavirin, or in patients with advanced immunosuppression. Symptoms typically resolve upon discontinuation of stavudine; in such cases, a reduced dosage may be cautiously restarted. Other potential adverse effects are pancreatitis, arthralgias, and elevation in serum aminotransferases. Lactic acidosis with hepatic steatosis, as well as lipodystrophy, appear to occur more frequently in patients receiving stavudine than in those receiving other NRTI agents. Moreover, because the co-administration of stavudine and didanosine may increase the incidence of lactic acidosis and pancreatitis, concurrent use should be avoided. This combination has been implicated in several deaths in HIV-infected pregnant women. A rare adverse effect is a rapidly progressive ascending neuromuscular weakness. Since zidovudine may reduce the phosphorylation of stavudine, these two drugs should not be used together. There is no evidence of human teratogenicity in those taking stavudine.

TENOFOVIR

Tenofovir is an acyclic nucleoside phosphonate (ie, nucleotide) analog of adenosine (Figure 49–2). Like the nucleoside analogs, tenofovir competitively inhibits HIV reverse transcriptase and causes chain termination after incorporation into DNA. However, only two rather than three intracellular phosphorylations are required for active inhibition of DNA synthesis. Tenofovir is also approved for the treatment of patients with HBV infection.

Tenofovir disoproxil fumarate is a water-soluble prodrug of active tenofovir. The oral bioavailability in fasted patients is approximately 25% and increases to 39% after a high-fat meal. The prolonged serum (12–17 hours) and intracellular half-lives allow once-daily dosing. Elimination occurs by both glomerular filtration and active tubular secretion.

Tenofovir is often co-administered with emtricitabine, and a once-daily, fixed-dose combination formulation is available, either alone or in combination with efavirenz. A recent placebo-controlled study found that use of emtricitabine and tenofovir was effective as preexposure prophylaxis, reducing HIV acquisition in men who have sex with men. In another placebo-controlled study, use of the experimental 1% tenofovir gel as a vaginal microbicide was effective in decreasing the incidence of heterosexual HIV acquisition.

The primary mutation associated with resistance to tenofovir is K65R.

Gastrointestinal complaints (eg, nausea, diarrhea, vomiting, flatulence) are the most common adverse effects but rarely require discontinuation of therapy. Since tenofovir is formulated with lactose, these may occur more frequently in patients with lactose intolerance. Other potential adverse effects include headache and asthenia. Tenofovir-associated proximal renal tubulopathy causes excessive renal phosphate and calcium losses and 1-hydroxylation defects of vitamin D, and preclinical studies in several animal species have demonstrated bone toxicity (eg, osteomalacia). Monitoring of bone mineral density should be considered with long-term use in those with risk factors for or with known osteoporosis, as well as in children. Reduction of renal function over time, as well as cases of acute renal failure and Fanconi's syndrome, have been reported in patients receiving tenofovir alone or in combination with emtricitabine. For this reason, tenofovir should be used with caution in patients at risk for renal dysfunction. Tenofovir may compete with other drugs that are actively secreted by the kidneys, such as cidofovir, acyclovir, and ganciclovir. Concurrent use of atazanavir or lopinavir/ritonavir may increase serum levels of tenofovir (Table 49–4).

Tenofovir is associated with decreased fetal growth and reduction in fetal bone porosity in monkeys. There is significant placental passage in humans.

ZALCITABINE

Zalcitabine (ddC) is a cytosine analog with high oral bioavailability (87%) and a serum half-life of 1–2 hours (Figure 49–2). An intracellular half-life of 2.6 hours necessitates thrice-daily dosing, which limits its usefulness. Plasma levels decrease by 25–39% when the drug is administered with food or antacids. The drug is excreted renally. Cerebrospinal fluid concentrations are approximately 20% of those in the plasma.

Although a variety of mutations associated with in vitro resistance to zalcitabine have been described, phenotypic resistance appears to be rare.

Zalcitabine therapy is associated with a dose-dependent peripheral neuropathy that can be treatment-limiting in 10–20% of patients but appears to be slowly reversible if treatment is stopped promptly. The potential for causing peripheral neuropathy constitutes a relative contraindication to use with other drugs that may cause neuropathy, including stavudine, didanosine, isoniazid, vincristine, and ribavirin. Decreased creatinine clearance or concurrent use of potential nephrotoxins (eg, amphotericin B, foscarnet, and aminoglycosides) may increase the risk of zalcitabine neuropathy, as does more advanced immunosuppression. The other major reported toxicity is oral and esophageal ulceration. Pancreatitis occurs less frequently than with didanosine administration, but co-administration of other drugs that cause pancreatitis may increase the frequency of this adverse effect. Headache, nausea, rash, and arthralgias may occur but tend to be mild or to resolve during therapy. Zalcitabine causes thymic lymphoma in rodents, as well as hydrocephalus at high doses; clinical relevance is unclear. The AUC of zalcitabine increases when co-administered with probenecid or cimetidine, and bioavailability decreases with concurrent antacids or metoclopramide. Lamivudine inhibits the phosphorylation of zalcitabine in vitro, potentially interfering with its efficacy.

ZIDOVUDINE

Zidovudine (**azidothymidine; AZT**) is a deoxythymidine analog (Figure 49–2) that is well absorbed (63%) and distributed to most body tissues and fluids, including the cerebrospinal fluid, where drug levels are 60–65% of those in serum. Although the serum

half-life averages 1 hour, the intracellular half-life of the phosphorylated compound is 3–4 hours, allowing twice-daily dosing. Zidovudine is eliminated primarily by renal excretion following glucuronidation in the liver.

Zidovudine is available in a fixed-dose combination formulation with lamivudine, either alone or in combination with abacavir.

Zidovudine was the first antiretroviral agent to be approved and has been well studied. The drug has been shown to decrease the rate of clinical disease progression and prolong survival in HIV-infected individuals. Efficacy has also been demonstrated in the treatment of HIV-associated dementia and thrombocytopenia. In pregnancy (Table 49–5), a regimen of oral zidovudine beginning between 14 and 34 weeks of gestation, intravenous zidovudine during labor, and zidovudine syrup to the neonate from birth through 6 weeks of age has been shown to reduce the rate of vertical (mother-to-newborn) transmission of HIV by up to 23%.

High-level zidovudine resistance is generally seen in strains with three or more of the five most common mutations: M41L, D67N, K70R, T215F, and K219Q. However, the emergence of certain mutations that confer decreased susceptibility to one drug (eg, L74V for didanosine and M184V for lamivudine) may enhance zidovudine susceptibility in previously zidovudine-resistant strains. Withdrawal of zidovudine may permit the reversion of zidovudine-resistant HIV-1 isolates to the susceptible wild-type phenotype.

The most common adverse effect of zidovudine is myelosuppression, resulting in macrocytic anemia (1–4%) or neutropenia (2–8%). Gastrointestinal intolerance, headaches, and insomnia may occur but tend to resolve during therapy. Lipoatrophy appears to be more common in patients receiving zidovudine or other thymidine analogs. Less common toxicities include thrombocytopenia, hyperpigmentation of the nails, and myopathy. High doses can cause anxiety, confusion, and tremulousness. Zidovudine causes vaginal neoplasms in mice; however, no human cases of genital neoplasms have been reported to date. Short-term safety has been demonstrated for both mother and infant.

TABLE 49–5 The use of antiretroviral agents in pregnancy.[1]

Recommended Agents	Alternate Agents
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	
Lamivudine, zidovudine	Abacavir, didanosine, emtricitabine, stavudine
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	
Nevirapine	
Protease inhibitors (PIs)	
Lopinavir/ritonavir	Atazanavir/ritonavir, indinavir/ritonavir, nelfinavir, ritonavir, saquinavir

[1]Data are insufficient to recommend the use of entry inhibitors or integrase inhibitors in pregnancy at the present time.

Increased serum levels of zidovudine may occur with concomitant administration of probenecid, phenytoin, methadone, fluconazole, atovaquone, valproic acid, and lamivudine, either through inhibition of first-pass metabolism or through decreased clearance. Zidovudine may decrease phenytoin levels. Hematologic toxicity may be increased during co-administration of other myelosuppressive drugs such as ganciclovir, ribavirin, and cytotoxic agents. Combination regimens containing zidovudine and stavudine should be avoided due to in vitro antagonism.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The NNRTIs bind directly to HIV-1 reverse transcriptase (Figure 49–4), resulting in allosteric inhibition of RNA- and DNA-dependent DNA polymerase activity. The binding site of NNRTIs is near to but distinct from that of NRTIs. Unlike the NRTI agents, NNRTIs neither compete with nucleoside triphosphates nor require phosphorylation to be active.

Baseline genotypic testing is recommended prior to initiating NNRTI treatment because primary resistance rates range from approximately 2% to 8%. NNRTI resistance occurs rapidly with monotherapy and can result from a single mutation. The K103N and Y181C mutations confer resistance across the entire class of NNRTIs, with the exception of the newest agent, etravirine. Other mutations (eg, L100I, Y188C, G190A) may confer cross-resistance among the NNRTI class. However, there is no cross-resistance between the NNRTIs and the NRTIs; in fact, some nucleoside-resistant viruses display hypersusceptibility to NNRTIs.

As a class, NNRTI agents tend to be associated with varying levels of gastrointestinal intolerance and skin rash, the latter of which may infrequently be serious (eg, Stevens-Johnson syndrome). A further limitation to use of NNRTI agents as a component of antiretroviral therapy is their metabolism by the CYP450 system, leading to innumerable potential drug-drug interactions (Tables 49–3 and 49–4). All NNRTI agents are substrates for CYP3A4 and can act as inducers (nevirapine), inhibitors (delavirdine), or mixed inducers and inhibitors (efavirenz, etravirine). Given the large number of non-HIV medications that are also metabolized by this pathway (see Chapter 4), drug-drug interactions must be expected and looked for; dosage adjustments are frequently required and some combinations are contraindicated.

DELAVIRDINE

Delavirdine has an oral bioavailability of about 85%, but this is reduced by antacids or H_2-blockers. It is extensively bound (~ 98%) to plasma proteins and has correspondingly low cerebrospinal fluid levels. Serum half-life is approximately 6 hours.

Skin rash occurs in up to 38% of patients receiving delavirdine; it typically occurs during the first 1–3 weeks of therapy and does not preclude rechallenge. However, severe rash such as erythema multiforme and Stevens-Johnson syndrome have rarely been reported. Other possible adverse effects are headache, fatigue, nausea, diarrhea, and increased serum aminotransferase levels.

Delavirdine has been shown to be teratogenic in rats, causing ventricular septal defects and other malformations at dosages not unlike those achieved in humans. Thus, pregnancy should be avoided when taking delavirdine.

Delavirdine is extensively metabolized by the CYP3A and CYP2D6 enzymes and also inhibits CYP3A4 and 2C9. Therefore, there are numerous potential drug-drug interactions to consider (Tables 49–3 and 49–4). The concurrent use of delavirdine with fosamprenavir and rifabutin is not recommended because of decreased delavirdine levels. Other medications likely to alter delavirdine levels include didanosine, lopinavir, nelfinavir, and ritonavir. Co-administration of delavirdine with indinavir or saquinavir prolongs the elimination half-life of these protease inhibitors, thus allowing them to be dosed twice rather than thrice daily.

EFAVIRENZ

Efavirenz can be given once daily because of its long half-life (40–55 hours). It is moderately well absorbed following oral administration (45%). Since toxicity may increase owing to increased bioavailability after a high-fat meal, efavirenz should be taken on an empty stomach. Efavirenz is principally metabolized by CYP3A4 and CYP2B6 to inactive hydroxylated metabolites; the remainder is eliminated in the feces as unchanged drug. It is highly bound to albumin (~ 99%), and cerebrospinal fluid levels range from 0.3% to 1.2% of plasma levels.

The principal adverse effects of efavirenz involve the central nervous system. Dizziness, drowsiness, insomnia, nightmares, and headache tend to diminish with continued therapy; dosing at bedtime may also be helpful. Psychiatric symptoms such as depression, mania, and psychosis have been observed and may necessitate discontinuation. Skin rash has also been reported early in therapy in up to 28% of patients; the rash is usually mild to moderate in severity and typically resolves despite continuation. Rarely, rash has been severe or life-threatening. Other potential adverse reactions are nausea, vomiting, diarrhea, crystalluria, elevated liver enzymes, and an increase in total serum cholesterol by 10–20%. High rates of fetal abnormalities occurred in pregnant monkeys exposed to efavirenz in doses roughly equivalent to the human dosage; several cases of congenital anomalies have been reported in humans. Therefore, efavirenz should be avoided in pregnant women, particularly in the first trimester.

As both an inducer and an inhibitor of CYP3A4, efavirenz induces its own metabolism and interacts with the metabolism of many other drugs (Tables 49–3 and 49–4). Since efavirenz may lower methadone levels, patients receiving these two agents concurrently should be monitored for signs of opioid withdrawal and may require an increased dose of methadone.

ETRAVIRINE

In 2008, etravirine was approved in the United States for use in treatment-experienced patients with HIV infection. Etravirine may be effective against strains of HIV that have developed resistance to first-generation NNRTIs, depending on the number of mutations present. Although etravirine has a higher genetic barrier to resistance than the other NNRTIs, mutations selected by etravirine usually are associated with resistance to efavirenz, nevirapine, and delavirdine.

The most common adverse effects of etravirine are rash, nausea, and diarrhea. The rash is typically mild and usually resolves after 1–2 weeks without discontinuation of therapy. Rarely, rash has been severe or life-threatening. Laboratory abnormalities include elevations in serum cholesterol, triglyceride, glucose, and hepatic transaminase levels. Transaminase elevations are more common in patients with HBV or HCV co-infection.

Etravirine is a substrate as well as an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19; it has many therapeutically significant drug-drug interactions (Tables 49–3 and 49–4). Some of the interactions are difficult to predict. For example, etravirine may decrease itraconazole and ketoconazole concentrations but increase voriconazole concentrations.

NEVIRAPINE

The oral bioavailability of nevirapine is excellent (> 90%) and is not food-dependent. The drug is highly lipophilic and achieves cerebrospinal fluid levels that are 45% of those in plasma. Serum half-life is 25–30 hours. It is extensively metabolized by the CYP3A isoform to hydroxylated metabolites and then excreted, primarily in the urine.

A single dose of nevirapine (200 mg) is effective in the prevention of transmission of HIV from mother to newborn when administered to women at the onset of labor and followed by a 2 mg/kg oral dose to the neonate within 3 days after delivery. There is no evidence of human teratogenicity. However, resistance has been documented after this single dose.

Rash, usually a maculopapular eruption that spares the palms and soles, occurs in up to 20% of patients, usually in the first 4–6 weeks of therapy. Although typically mild and self-limited, rash is dose-limiting in about 7% of patients. Women appear to have an increased incidence of rash. When initiating therapy, gradual dose escalation over 14 days is recommended to decrease the incidence of rash. Severe and life-threatening skin rashes have been rarely reported, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Nevirapine therapy should be immediately discontinued in patients with severe rash and in those with accompanying constitutional symptoms; since rash may accompany hepatotoxicity, liver function tests should be assessed. Symptomatic liver toxicity may occur in up to 4% of patients and is more frequent in those with higher pretherapy CD4 cell counts (ie, > 250 cells/mm^3 in women and > 400 cells/mm^3 in men), in women, and in those with HBV or HCV co-infection. Fulminant, life-threatening hepatitis has been reported, typically within the first 18 weeks of therapy. Other adverse effects include fever, nausea, headache, and somnolence.

Nevirapine is a moderate inducer of CYP3A metabolism, resulting in decreased levels of amprenavir, indinavir, lopinavir,

saquinavir, efavirenz, and methadone. Drugs that induce the CYP3A system, such as rifampin, rifabutin, and St. John's wort, can decrease levels of nevirapine, whereas those that inhibit CYP3A activity, such as fluconazole, ketoconazole, and clarithromycin, can increase nevirapine levels. Since nevirapine may lower methadone levels, patients receiving these two agents concurrently should be monitored for signs of opioid withdrawal and may require an increased dose of methadone.

PROTEASE INHIBITORS

During the later stages of the HIV growth cycle, the *gag* and *gag-pol* gene products are translated into polyproteins, and these become immature budding particles. The HIV protease is responsible for cleaving these precursor molecules to produce the final structural proteins of the mature virion core. By preventing post-translational cleavage of the Gag-Pol polyprotein, protease inhibitors (PIs) prevent the processing of viral proteins into functional conformations, resulting in the production of immature, noninfectious viral particles (Figure 49–4). Unlike the NRTIs, PIs do not need intracellular activation.

Specific genotypic alterations that confer phenotypic resistance are fairly common with these agents, thus contraindicating monotherapy. Some of the most common mutations conferring broad resistance to PIs are substitutions at the 10, 46, 54, 82, 84, and 90 codons; the number of mutations may predict the level of phenotypic resistance. The I50L substitution emerging during atazanavir therapy has been associated with *increased* susceptibility to other PIs. Darunavir and tipranavir appear to have improved virologic activity in patients harboring HIV-1 resistant to other PIs.

A syndrome of redistribution and accumulation of body fat that results in central obesity, dorsocervical fat enlargement (buffalo hump), peripheral and facial wasting, breast enlargement, and a cushingoid appearance has been observed in patients receiving antiretroviral therapy. These abnormalities may be particularly associated with the use of PIs, although the recently licensed atazanavir appears to be an exception (see below). Concurrent increases in triglyceride and low-density lipoprotein levels, along with hyperglycemia and insulin resistance, have also been noted. The cause is not yet known.

Whether PI agents are associated with bone loss and osteoporosis after long-term use is controversial and under investigation. PIs have been associated with increased spontaneous bleeding in patients with hemophilia A or B; an increased risk of intracranial hemorrhage has been reported in patients receiving tipranavir with ritonavir.

The concurrent use of saquinavir and ritonavir has recently been found to be associated with QT and PR interval prolongation, and is contraindicated. QT prolongation may result in life-threatening torsades de pointes arrhythmia.

All of the antiretroviral PIs are extensively metabolized by CYP3A4, with ritonavir having the most pronounced inhibitory effect and saquinavir the least. Some PI agents, such as amprenavir and ritonavir, are also inducers of specific CYP isoforms. As a result, there is enormous potential for drug-drug interactions with other antiretroviral agents and other commonly used medications (Tables 49–3 and 49–4). Expert resources about drug-drug interactions should be consulted, as dosage adjustments are frequently required and some combinations are contraindicated. It is noteworthy that the potent CYP3A4 inhibitory properties of ritonavir are used to clinical advantage by having it "boost" the levels of other PI agents when given in combination, thus acting as a pharmacokinetic enhancer rather than an antiretroviral agent. Ritonavir boosting increases drug exposure, thereby prolonging the drug's half-life and allowing reduction in frequency; in addition, the genetic barrier to resistance is raised.

ATAZANAVIR

Atazanavir is an azapeptide PI with a pharmacokinetic profile that allows once-daily dosing. It should be taken with a light meal to enhance bioavailability. Atazanavir requires an acidic medium for absorption and exhibits pH-dependent aqueous solubility; therefore, separation of ingestion from acid-reducing agents by at least 12 hours is recommended and concurrent proton pump inhibitors are contraindicated. Atazanavir is able to penetrate both the cerebrospinal and seminal fluids. The plasma half-life is 6–7 hours, which increases to approximately 11 hours when co-administered with ritonavir. The primary route of elimination is biliary; atazanavir should not be given to patients with severe hepatic insufficiency.

Resistance to atazanavir has been associated with various known PI mutations as well as with the novel I50L substitution. Whereas some atazanavir resistance mutations have been associated in vitro with decreased susceptibility to other PIs, the I50L mutation has been associated with increased susceptibility to other PIs.

The most common adverse effects in patients receiving atazanavir are diarrhea and nausea; vomiting, abdominal pain, headache, peripheral neuropathy, and skin rash may also occur. As with indinavir, indirect hyperbilirubinemia with overt jaundice may occur in approximately 10% of patients, owing to inhibition of the UGT1A1 glucuronidation enzyme. Elevation of hepatic enzymes has also been observed, usually in patients with underlying HBV or HCV co-infection. Nephrolithiasis has recently been described in association with atazanavir use. In contrast to the other PIs, atazanavir does not appear to be associated with dyslipidemia, fat redistribution, or the metabolic syndrome. Atazanavir may be associated with prolongation of the electrocardiographic PR interval, which is usually inconsequential but may be exacerbated by other causative agents such as calcium channel blockers and may result in AV block QT prolongation is another potential electrocardiographic effect of atazanavir but is rarely clinically significant.

As an inhibitor of CYP3A4 and CYP2C9, the potential for drug-drug interactions with atazanavir is great (Tables 49–3 and 49–4). Atazanavir AUC is reduced by up to 76% when combined with a proton pump inhibitor; thus, these combinations are to be avoided. In addition, co-administration of atazanavir with other drugs that inhibit UGT1A1, such as irinotecan, may increase its levels. Tenofovir and efavirenz should not be co-administered with atazanavir unless ritonavir is added to boost levels.

DARUNAVIR

Darunavir is licensed as a PI that must be co-administered with ritonavir. It was initially licensed for use in treatment-experienced patients only; thus there is less clinical experience with its use in treatment-naïve patients. Darunavir may be administered once daily in treatment-naïve patients.

Symptomatic adverse effects of darunavir include diarrhea, nausea, headache, and rash. Laboratory abnormalities include dyslipidemia (though possibly less frequent than with other boosted PI regimens) and increases in amylase and hepatic transaminase levels. Liver toxicity, including severe hepatitis, has been reported in some patients taking darunavir; the risk of hepatotoxicity may be higher for persons with HBV, HCV, or other chronic liver disease.

Darunavir contains a sulfonamide moiety and should be used cautiously in patients with sulfonamide allergy.

Darunavir both inhibits and is metabolized by the CYP3A enzyme system, conferring many possible drug-drug interactions (Tables 49–3 and 49–4). In addition, the co-administered ritonavir is a potent inhibitor of CYP3A and CYP2D6, and an inducer of other hepatic enzyme systems.

FOSAMPRENAVIR

Fosamprenavir is a prodrug of amprenavir that is rapidly hydrolyzed by enzymes in the intestinal epithelium. Because of its significantly lower daily pill burden, fosamprenavir tablets have replaced amprenavir capsules for adults. Fosamprenavir is most often administered in combination with low-dose ritonavir.

Amprenavir is rapidly absorbed from the gastrointestinal tract, and its prodrug can be taken with or without food. However, high-fat meals decrease absorption and thus should be avoided. The plasma half-life is relatively long (7–11 hours). Amprenavir is metabolized in the liver by CYP3A4 and should be used with caution in the setting of hepatic insufficiency.

The most common adverse effects of fosamprenavir are headache, nausea, diarrhea, perioral paresthesias, depression, and rash. Up to 3% of patients may experience rashes (including Stevens-Johnson syndrome) severe enough to warrant drug discontinuation.

Amprenavir is both an inducer and an inhibitor of CYP3A4 and is contraindicated with numerous drugs (Tables 49–3 and 49–4). The oral solution, which contains propylene glycol, is contraindicated in young children, pregnant women, patients with renal or hepatic failure, and those using metronidazole or disulfiram. Also, the oral solutions of amprenavir and ritonavir should not be co-administered because the propylene glycol in one and the ethanol in the other may compete for the same metabolic pathway, leading to accumulation of either. Because the oral solution also contains vitamin E at several times the recommended daily dosage, supplemental vitamin E should be avoided. Amprenavir, a sulfonamide, is contraindicated in patients with a history of sulfa allergy. Lopinavir/ritonavir should not be co-administered with amprenavir owing to decreased amprenavir and altered lopinavir exposures. An increased dosage of amprenavir is recommended when co-administered with efavirenz (with or without the addition of ritonavir to boost levels).

INDINAVIR

Indinavir requires an acidic environment for optimum solubility and therefore must be consumed on an empty stomach or with a small, low-fat, low-protein meal for maximal absorption (60–65%). The serum half-life is 1.5–2 hours, protein binding is approximately 60%, and the drug has a high level of cerebrospinal fluid penetration (up to 76% of serum levels). Excretion is primarily fecal. An increase in AUC by 60% and in half-life to 2.8 hours in the setting of hepatic insufficiency necessitates dose reduction.

The most common adverse effects of indinavir are indirect hyperbilirubinemia and nephrolithiasis due to urinary crystallization of the drug. Nephrolithiasis can occur within days after initiating therapy, with an estimated incidence of approximately 10%. Consumption of at least 48 ounces of water daily is important to maintain adequate hydration. Thrombocytopenia, elevations of serum aminotransferase levels, nausea, diarrhea, insomnia, dry throat, dry skin, and indirect hyperbilirubinemia have also been reported. Insulin resistance may be more common with indinavir than with the other PIs, occurring in 3–5% of patients. There have also been rare cases of acute hemolytic anemia. In rats, high doses of indinavir are associated with development of thyroid adenomas.

Since indinavir is an inhibitor of CYP3A4, numerous and complex drug interactions can occur (Tables 49–3 and 49–4). Combination with ritonavir (boosting) allows for twice-daily rather than thrice-daily dosing and eliminates the food restriction associated with use of indinavir. However, there is potential for an increase in nephrolithiasis with this combination compared with indinavir alone; thus, a high fluid intake (1.5–2 L/d) is advised.

LOPINAVIR

Lopinavir is currently formulated only in combination with ritonavir, which inhibits the CYP3A-mediated metabolism of lopinavir, thereby resulting in increased exposure to lopinavir. In addition to improved patient compliance due to reduced pill burden, lopinavir/ritonavir is generally well tolerated.

Lopinavir should be taken with food to enhance bioavailability. The drug is highly protein bound (98–99%), and its half-life is 5–6 hours. Lopinavir is extensively metabolized by CYP3A, which is inhibited by ritonavir. Serum levels of lopinavir may be increased in patients with hepatic impairment.

The most common adverse effects of lopinavir are diarrhea, abdominal pain, nausea, vomiting, and asthenia. Elevations in serum cholesterol and triglycerides are common. Potential drug-drug interactions are extensive (Tables 49–3 and 49–4). Increased dosage of lopinavir/ritonavir is recommended when co-administered with efavirenz or nevirapine, which induce lopinavir metabolism. Concurrent use of fosamprenavir should be avoided owing to altered

exposure to lopinavir with decreased levels of amprenavir. Also, concomitant use of lopinavir/ritonavir and rifampin is contraindicated due to an increased risk for hepatotoxicity. Since the oral solution of lopinavir/ritonavir contains alcohol, concurrent disulfiram and metronidazole are contraindicated. There is no evidence of human teratogenicity of lopinavir/ritonavir; short-term safety in pregnant women has been demonstrated for mother and infant.

NELFINAVIR

Nelfinavir has high absorption in the fed state (70–80%), undergoes metabolism by CYP3A, and is excreted primarily in the feces. The plasma half-life in humans is 3.5–5 hours, and the drug is more than 98% protein-bound.

The most common adverse effects associated with nelfinavir are diarrhea and flatulence. Diarrhea often responds to antidiarrheal medications but can be dose-limiting. Nelfinavir is an inhibitor of the CYP3A system, and multiple drug interactions may occur (Tables 49–3 and 49–4). An increased dosage of nelfinavir is recommended when co-administered with rifabutin (with a decreased dose of rifabutin), whereas a decrease in saquinavir dose is suggested with concurrent nelfinavir. Co-administration with efavirenz should be avoided due to decreased nelfinavir levels. Nelfinavir has a favorable safety and pharmacokinetic profile for pregnant women compared with that of other PIs (Table 49–5); there is no evidence of human teratogenicity.

RITONAVIR

Ritonavir has a high bioavailability (about 75%) that increases with food. It is 98% protein-bound and has a serum half-life of 3–5 hours. Metabolism to an active metabolite occurs via the CYP3A and CYP2D6 isoforms; excretion is primarily in the feces. Caution is advised when administering the drug to persons with impaired hepatic function.

Potential adverse effects of ritonavir, particularly when administered at full dosage, are gastrointestinal disturbances, paresthesias (circumoral or peripheral), elevated serum aminotransferase levels, altered taste, headache, and elevations in serum creatine kinase. Nausea, vomiting, diarrhea, or abdominal pain typically occur during the first few weeks of therapy but may diminish over time or if the drug is taken with meals. Dose escalation over 1–2 weeks is recommended to decrease the dose-limiting side effects. Liver adenomas and carcinomas have been induced in male mice receiving ritonavir; no similar effects have been observed to date in humans.

Ritonavir is a potent inhibitor of CYP3A4, resulting in many potential drug interactions (Tables 49–3 and 49–4). However, this characteristic has been used to great advantage when ritonavir is administered in low doses (100–200 mg twice daily) in combination with any of the other PI agents, in that increased blood levels of the latter agents permit lower or less frequent dosing (or both) with greater tolerability as well as the potential for greater efficacy against resistant virus. Therapeutic levels of digoxin and theophylline should be monitored when co-administered with ritonavir owing to a likely increase in their concentrations. The concurrent use of saquinavir and ritonavir is contraindicated due to an increased risk of QT prolongation (with torsades de pointes arrhythmia) and PR interval prolongation. There is limited experience with full-dose ritonavir during pregnancy to date; however, low-dose ritonavir as a "booster" has appeared to be well tolerated in mother and infant.

SAQUINAVIR

In its original formulation as a hard gel capsule (saquinavir-H; Invirase), oral saquinavir was poorly bioavailable (only about 4% after food). However, reformulation of saquinavir-H for once-daily dosing in combination with low-dose ritonavir has both improved antiviral efficacy and decreased gastrointestinal adverse effects.

Saquinavir should be taken within 2 hours after a fatty meal for enhanced absorption. Saquinavir is 97% protein-bound, and serum half-life is approximately 2 hours. Saquinavir has a large volume of distribution, but penetration into the cerebrospinal fluid is negligible. Excretion is primarily in the feces. Reported adverse effects include gastrointestinal discomfort (nausea, diarrhea, abdominal discomfort, dyspepsia) and rhinitis. When administered in combination with low-dose ritonavir, there appears to be less dyslipidemia or gastrointestinal toxicity than with some of the other boosted PI regimens. However, the concurrent use of saquinavir and ritonavir is newly recognized to confer an increased risk of QT prolongation (with torsades de pointes arrhythmia) and PR interval prolongation.

Saquinavir is subject to extensive first-pass metabolism by CYP3A4 and functions as a CYP3A4 inhibitor as well as a substrate; thus, there are many potential drug-drug interactions (Tables 49–3 and 49–4). A decreased dose of saquinavir is recommended when co-administered with nelfinavir. Increased saquinavir levels when co-administered with omeprazole necessitate close monitoring for toxicities. Digoxin levels may increase if co-administered with saquinavir and should therefore be monitored. Liver function tests should be monitored if saquinavir is co-administered with delavirdine or rifampin. There is no evidence of human teratogenicity from saquinavir; there is short-term safety data for both mother and infant.

TIPRANAVIR

Tipranavir is a newer PI indicated for use in treatment-experienced HIV-1-infected patients who harbor strains resistant to other PI agents. It is used in combination with ritonavir to achieve effective serum levels and is not approved for treatment-naïve patients.

Bioavailability is poor but is increased when taken with a high-fat meal. The drug is metabolized by the liver microsomal system and is contraindicated in patients with hepatic insufficiency. Tipranavir contains a sulfonamide moiety and should not be administered to patients with known sulfa allergy.

The most common adverse effects from tipranavir are diarrhea, nausea, vomiting, and abdominal pain. An urticarial or maculopapular rash is more common in women and may be accompanied

by systemic symptoms or desquamation. Liver toxicity, including life-threatening hepatic decompensation, has been observed and is more common in patients with chronic HBV or HCV infection. Tipranavir should be discontinued in patients who have increased serum transaminase levels that are more than 10 times the upper limit of normal or more than 5 times normal in combination with increased serum bilirubin. Because of an increased risk for intracranial hemorrhage in patients receiving tipranavir/ritonavir, the drug should be avoided in patients with head trauma or bleeding diathesis. Other potential adverse effects include depression, elevation in amylase, and decreased white blood cell count.

Tipranavir both inhibits and induces the CYP3A4 system. When used in combination with ritonavir, its net effect is inhibition. Tipranavir also induces P-glycoprotein transporter and thus may alter the disposition of many other drugs (Table 49–4). Concurrent administration of tipranavir with fosamprenavir or saquinavir should be avoided owing to decreased blood levels of the latter drugs. Tipranavir/ritonavir may also decrease serum levels of valproic acid and omeprazole. Levels of lovastatin, simvastatin, atorvastatin, and rosuvastatin may be increased, increasing the risk for rhabdomyolysis and myopathy. Tipranavir contains a sulfonamide moiety and should be used cautiously in patients with sulfonamide allergy.

ENTRY INHIBITORS

The process of HIV-1 entry into host cells is complex; each step presents a potential target for inhibition. Viral attachment to the host cell entails binding of the viral envelope glycoprotein complex gp160 (consisting of gp120 and gp41) to its cellular receptor CD4. This binding induces conformational changes in gp120 that enable access to the chemokine receptors CCR5 or CXCR4. Chemokine receptor binding induces further conformational changes in gp120, allowing exposure to gp41 and leading to fusion of the viral envelope with the host cell membrane and subsequent entry of the viral core into the cellular cytoplasm.

ENFUVIRTIDE

Enfuvirtide is a synthetic 36-amino-acid peptide fusion inhibitor that blocks HIV entry into the cell (Figure 49–4). Enfuvirtide binds to the gp41 subunit of the viral envelope glycoprotein, preventing the conformational changes required for the fusion of the viral and cellular membranes. Enfuvirtide, which must be administered by subcutaneous injection, is the only parenterally administered antiretroviral agent. Metabolism appears to be by proteolytic hydrolysis without involvement of the CYP450 system. Elimination half-life is 3.8 hours.

Resistance to enfuvirtide can result from mutations in gp41; the frequency and significance of this phenomenon are being investigated. However, enfuvirtide lacks cross-resistance with the other currently approved antiretroviral drug classes.

The most common adverse effects associated with enfuvirtide therapy are local injection site reactions, consisting of painful erythematous nodules. Although frequent, these are typically mild to moderate and rarely lead to discontinuation. Other symptomatic side effects may include insomnia, headache, dizziness, and nausea. Hypersensitivity reactions may rarely occur, are of varying severity, and may recur on rechallenge. Eosinophilia is the primary laboratory abnormality seen with enfuvirtide administration. In prospective clinical trials, an increased rate of bacterial pneumonia was noted in patients receiving enfuvirtide. No drug-drug interactions have been identified that would require the alteration of the dosage of concomitant antiretroviral or other drugs.

MARAVIROC

Maraviroc binds specifically and selectively to the host protein CCR5, one of two chemokine receptors necessary for entrance of HIV into CD4+ cells. Maraviroc is approved for adults with CCR5-tropic (also known as R5) HIV-1 infection who are experiencing virologic failure due to resistance to other antiretroviral agents. Studies have shown that 52–60% of patients in whom at least two antiviral regimens had failed were infected with R5 HIV. Since maraviroc is active against HIV that uses the CCR5 co-receptor exclusively, and not against HIV strains with CXCR4, dual, or mixed tropism, tropism testing should be performed before initiating treatment with maraviroc. Clinical experience with the use of maraviroc in treatment-naïve patients is limited.

The absorption of maraviroc is rapid but variable, with the time to maximum absorption generally being 1–4 hours after ingestion of the drug. Most of the drug (≥ 75%) is excreted in the feces, whereas approximately 20% is excreted in urine. The recommended dose of maraviroc varies according to renal function and the concomitant use of CYP3A inducers or inhibitors. Maraviroc is contraindicated in patients with severe or end-stage renal impairment who are taking concurrent CYP3A inhibitors or inducers, and caution is advised when used in patients with preexisting hepatic impairment and in those co-infected with HBV or HCV. Maraviroc has been shown to have excellent penetration into the cervicovaginal fluid, with levels almost four times higher than the corresponding concentrations in blood plasma.

Resistance to maraviroc is associated with one or more mutations in the V3 loop of gp120. There appears to be no cross-resistance with drugs from any other class, including the fusion inhibitor enfuvirtide. However, virologic failure of regimens containing maraviroc may potentially be caused by emergence of non–CCR5-tropic virus (eg, CXCR4-tropic virus) or by changes in viral tropism, owing to the development of multiple mutations throughout gp160.

Maraviroc is a substrate for CYP3A4 and therefore requires adjustment in the presence of drugs that interact with these enzymes (Tables 49–3 and 49–4). It is also a substrate for P-glycoprotein, which limits intracellular concentrations of the drug. The dosage of maraviroc must be decreased if it is co-administered with strong CYP3A inhibitors (eg, delavirdine, ketoconazole, itraconazole, clarithromycin, or any protease inhibitor other than tipranavir) and must be increased if co-administered with CYP3A inducers (eg, efavirenz, etravirine, rifampin, carbamazepine, phenytoin, or St. John's wort).

Potential adverse effects include cough, upper respiratory tract infections, postural hypotension (particularly in the setting of renal insufficiency), muscle and joint pain, abdominal pain, diarrhea, and sleep disturbance. Due to reports of hepatotoxicity, which may be preceded by evidence of a systemic allergic reaction (ie, pruritic rash, eosinophilia, or elevated IgE), discontinuation of maraviroc should be considered promptly if this constellation of signs occurs. Myocardial ischemia and infarction have been observed in patients receiving maraviroc; therefore caution is advised in patients at increased cardiovascular risk.

There has been some concern that blockade of the chemokine CCR5 receptor—a human protein—may result in decreased immune surveillance, with a subsequent increased risk of malignancy (eg, lymphoma) or infection. To date, however, there has been no evidence of an increased risk of either malignancy or infection in patients receiving maraviroc.

INTEGRASE STRAND TRANSFER INHIBITORS

RALTEGRAVIR

Raltegravir is a pyrimidinone analog that binds integrase, a viral enzyme essential to the replication of both HIV-1 and HIV-2. By doing so, it inhibits strand transfer, the third and final step of provirus integration, thus interfering with the integration of reverse-transcribed HIV DNA into the chromosomes of host cells (Figure 49–4). It was initially licensed for use in treatment-experienced adult patients infected with strains of HIV-1 resistant to multiple other agents, but more recently has received approval for use in initial therapy as well. However, clinical experience is limited in treatment-naïve patients.

Absolute bioavailability of raltegravir has not been established but does not appear to be food-dependent. The drug is metabolized by glucuronidation and does not interact with the cytochrome P450 system; therefore, it is expected to have fewer drug-drug interactions than many of the other antiretroviral agents. However, in combination with rifampin, a strong inducer of UDP-glucuronosyl transferase 1A1 (UGT1A1), the dose of raltegravir should be increased from 400 mg twice daily to 800 mg twice daily. Since polyvalent cations (eg, magnesium, calcium, and iron) may bind integrase inhibitors and interfere with their activity, antacids should be used cautiously and taken separately from raltegravir.

Although virologic failure has been uncommon in clinical trials of raltegravir to date, in vitro resistance requires only a single point mutation (eg, at codons 148 or 155). The low genetic barrier to resistance emphasizes the importance of combination therapies and of adherence. Integrase mutations are not expected to affect sensitivity to other classes of antiretroviral agents.

Potential adverse effects of raltegravir include insomnia, headache, diarrhea, nausea, dizziness, and fatigue. Increases in creatine kinase may occur, with potential myopathy or rhabdomyolysis; there is minimal effect on serum lipids.

NEW & INVESTIGATIONAL ANTIRETROVIRAL AGENTS

New therapies are continually being sought that exploit other HIV targets, have activity against resistant viral strains, have a lower incidence of adverse effects, and offer convenient dosing. Newly approved agents and those currently in advanced stages of clinical development include the NRTI agents **elvucitabine, racivir,** and **apricitabine;** the NNRTI agent **rilpivirine;** entry inhibitors such as the CCR5 receptor antagonists **vicriviroc** and **PRO 140,** the fusion inhibitor **TNX-355 (ibalizumab**); and integrase inhibitors such as **elvitegravir.** In addition, new drug classes such as maturation inhibitors **(bevirimat)** are under investigation.

■ ANTIHEPATITIS AGENTS

Several agents effective against HBV and HCV are now available (Table 49–6). Current treatment is suppressive rather than curative and the high prevalence of these infections worldwide, with their concomitant morbidity and mortality, reflect a critical need for improved therapeutics.

INTERFERON ALFA

Interferons are host cytokines that exert complex antiviral, immunomodulatory, and antiproliferative actions (see Chapter 55). Interferon alfa appears to function by induction of intracellular signals following binding to specific cell membrane receptors, resulting in inhibition of viral penetration, translation, transcription, protein processing, maturation, and release, as well as increased host expression of major histocompatibility complex antigens, enhanced phagocytic activity of macrophages, and augmentation of the proliferation and survival of cytotoxic T cells.

Injectable preparations of interferon alfa are available for treatment of both HBV and HCV infections (Table 49–6). Interferon alfa-2a and interferon alfa-2b may be administered either subcutaneously or intramuscularly; interferon alfacon-1 is administered subcutaneously. Elimination half-life is 2–5 hours for interferon alfa-2a and -2b, depending on the route of administration. The half-life of interferon alfacon-1 in patients with chronic HCV ranges from 6 to 10 hours. Alfa interferons are filtered at the glomerulus and undergo rapid proteolytic degradation during tubular reabsorption, such that detection in the systemic circulation is negligible. Liver metabolism and subsequent biliary excretion are considered minor pathways.

A meta-analysis of clinical trials in patients with chronic HBV infection showed that treatment with interferon alfa is associated with a higher incidence of hepatitis e antigen (HBeAg) seroconversion and undetectable HBV DNA levels compared with placebo. The addition of the pegylated moiety results in further increases in the proportion of patients with HBeAg seroconversion (~ 30%) and a decline by approximately 4 log copies/mL (a 99.99% reduction) in HBV DNA after 1 year.

TABLE 49–6 Drugs used to treat viral hepatitis.

Agent	Indication	Recommended Adult Dosage	Route of Administration
Hepatitis B			
Lamivudine[1]	Chronic hepatitis B	100 mg once daily (150 mg once daily if co-infection with HIV is present)	Oral
Adefovir[1]	Chronic hepatitis B	10 mg once daily	Oral
Entecavir[1]	Chronic hepatitis B	0.5–1 mg once daily	Oral
Tenofovir[1]	Chronic hepatitis B	300 mg once daily	Oral
Telbivudine[1]	Chronic hepatitis B	600 mg once daily	Oral
Interferon alfa-2b	Chronic hepatitis B	5 million units once daily or 10 million units three times weekly	Subcutaneous or intramuscular
Pegylated interferon alfa-2a[1]	Chronic hepatitis B	180 mcg once weekly	Subcutaneous
Hepatitis C			
Pegylated interferon alfa-2a[1]	Chronic hepatitis C	180 mcg once weekly plus ribavirin (800–1200 mg/d)	Subcutaneous
Pegylated interferon alfa-2b[1]	Chronic hepatitis C	1.5 mcg/kg once weekly with ribavirin (800–1200 mg/d)	Subcutaneous
Interferon alfa-2b[1]	Acute hepatitis C	5 million units once daily for 3–4 weeks, then 5 million units three times weekly	Subcutaneous or intramuscular

[1]Dose must be reduced in patients with renal insufficiency.

The use of pegylated (polyethylene glycol-complexed) interferon alfa-2a and pegylated interferon alfa-2b results in slower clearance and longer terminal half-lives and steadier concentrations, which allows for less frequent dosing in patients with chronic HCV infection. Renal elimination accounts for about 30% of clearance, and clearance is approximately halved in subjects with impaired renal function; dosage must therefore be adjusted.

The adverse effects of interferon alfa include a flu-like syndrome (ie, headache, fevers, chills, myalgias, and malaise) that typically occurs within 6 hours after dosing; this syndrome occurs in more than 30% of patients during the first week of therapy and tends to resolve upon continued administration. Transient hepatic enzyme elevations may occur in the first 8–12 weeks of therapy and appear to be more common in responders. Potential adverse effects during chronic therapy include neurotoxicities (mood disorders, depression, somnolence, confusion, seizures), myelosuppression, profound fatigue, weight loss, rash, cough, myalgia, alopecia, tinnitus, reversible hearing loss, retinopathy, pneumonitis, and possibly cardiotoxicity. Induction of autoantibodies may occur, causing exacerbation or unmasking of autoimmune disease (particularly thyroiditis). The polyethylene glycol molecule is a nontoxic polymer that is readily excreted in the urine.

Contraindications to interferon alfa therapy include hepatic decompensation, autoimmune disease, and history of cardiac arrhythmia. Caution is advised in the setting of psychiatric disease, epilepsy, thyroid disease, ischemic cardiac disease, severe renal insufficiency, and cytopenia. Alfa interferons are abortifacient in primates and should not be administered in pregnancy. Potential drug-drug interactions include increased theophylline and methadone levels. Co-administration with didanosine is not recommended because of a risk of hepatic failure, and co-administration with zidovudine may exacerbate cytopenias.

TREATMENT OF HEPATITIS B VIRUS INFECTION

The goals of chronic HBV therapy are to sustain suppression of HBV replication, resulting in slowing of progression of hepatic disease (with retardation of hepatic fibrosis and even reversal of cirrhosis), prevention of complications (ie, cirrhosis, hepatic failure, and hepatocellular carcinoma), and reduction of the need for liver transplantation. This translates into suppression of HBV DNA to undetectable levels, seroconversion of HBeAg (or more rarely, HBsAg) from positive to negative, and reduction in elevated hepatic transaminase levels. These end points are correlated with improvement in necroinflammatory disease, a decreased risk of hepatocellular carcinoma and cirrhosis, and a decreased need for liver transplantation. All the currently licensed therapies achieve these goals. However, because current therapies suppress HBV replication without eradicating the virus, initial responses may not be durable. The covalently closed circular (ccc) viral DNA exists in stable form indefinitely within the cell, serving as a reservoir for HBV throughout the life of the cell and resulting in the capacity to reactivate. Relapse is more common in patients co-infected with HBV and hepatitis D virus.

As of 2010 seven drugs were approved for treatment of chronic HBV infection in the United States: five oral nucleoside/nucleotide analogs (lamivudine, adefovir dipivoxil, tenofovir, entecavir, telbivudine) and two injectable interferon drugs (interferon alfa-2b, pegylated interferon alfa-2a) (Table 49–6). The use of interferon has been supplanted by long-acting pegylated interferon, allowing

once-weekly rather than daily or thrice-weekly dosing. In general, nucleoside/nucleotide analog therapies have better tolerability and ultimately produce a higher response rate than the interferons (though less rapid); however, response may be less sustained after discontinuation of the nucleoside/nucleotide therapies, and emergence of resistance may be problematic. The nucleotides are effective in nucleoside resistance and vice versa. In addition, oral agents may be used in patients with decompensated liver disease, and the therapy is chronic rather than finite as with interferon therapy.

Several anti-HBV agents have anti-HIV activity as well, including lamivudine, adefovir dipivoxil, and tenofovir. Emtricitabine, an antiretroviral NRTI, is under clinical evaluation for HBV treatment in combination with tenofovir, which may be particularly suited to individuals co-infected with HIV and HBV. Because NRTI agents may be used in patients co-infected with HBV and HIV, it is important to note that acute exacerbation of hepatitis may occur upon discontinuation or interruption of these agents.

ADEFOVIR DIPIVOXIL

Although initially and abortively developed for treatment of HIV infection, adefovir dipivoxil gained approval, at lower and less toxic doses, for treatment of HBV infection. Adefovir dipivoxil is the diester prodrug of adefovir, an acyclic phosphonated adenine nucleotide analog (Figure 49–2). It is phosphorylated by cellular kinases to the active diphosphate metabolite and then competitively inhibits HBV DNA polymerase and causes chain termination after incorporation into viral DNA. Adefovir is active in vitro against a wide range of DNA and RNA viruses, including HBV, HIV, and herpesviruses.

Oral bioavailability of adefovir dipivoxil is about 59% and is unaffected by meals; it is rapidly and completely hydrolyzed to the parent compound by intestinal and blood esterases. Protein binding is low (< 5%). The intracellular half-life of the diphosphate is prolonged, ranging from 5 to 18 hours in various cells; this makes once-daily dosing feasible. Adefovir is excreted by a combination of glomerular filtration and active tubular secretion and requires dose adjustment for renal dysfunction; however, it may be administered to patients with decompensated liver disease.

Of the oral agents, adefovir may be slower to suppress HBV DNA levels and the least likely to induce HBeAg seroconversion. Although emergence of resistance is rare during the first year of therapy, it approaches 30% at the end of 4 years. Naturally occurring (ie, primary) adefovir-resistant rt233 HBV mutants have recently been described. There is no cross-resistance between adefovir and lamivudine.

Adefovir dipivoxil is well tolerated. A dose-dependent nephrotoxicity has been observed in clinical trials, manifested by increased serum creatinine with decreased serum phosphorous and more common in patients with baseline renal insufficiency and those receiving high doses (60 mg/d). Other potential adverse effects are headache, diarrhea, asthenia, and abdominal pain. As with other NRTI agents, lactic acidosis and hepatic steatosis are considered a risk owing to mitochondrial dysfunction. No clinically important drug-drug interactions have been recognized to date; however, co-administration with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of adefovir or the co-administered drug. Pivalic acid, a by-product of adefovir dipivoxil metabolism, can esterify free carnitine and result in decreased carnitine levels. However, it is not felt necessary to administer carnitine supplementation with the low doses used to treat patients with HBV (10 mg/d). Adefovir is embryotoxic in rats at high doses and is genotoxic in preclinical studies.

ENTECAVIR

Entecavir is an orally administered guanosine nucleoside analog (Figure 49–2) that competitively inhibits all three functions of HBV DNA polymerase, including base priming, reverse transcription of the negative strand, and synthesis of the positive strand of HBV DNA. Oral bioavailability approaches 100% but is decreased by food; therefore, entecavir should be taken on an empty stomach. The intracellular half-life of the active phosphorylated compound is 15 hours. It is excreted by the kidney, undergoing both glomerular filtration and net tubular secretion.

Comparison with lamivudine in patients with chronic HBV infection demonstrated similar rates of HBeAg seroconversion but significantly higher rates of HBV DNA viral suppression with entecavir, normalization of serum alanine aminotransferase levels, and histologic improvement in the liver. Entecavir appears to have a higher barrier to the emergence of resistance than lamivudine. Although selection of resistant isolates with the S202G mutation has been documented during therapy, clinical resistance is rare (< 1% at 4 years). Also, decreased susceptibility to entecavir may occur in association with lamivudine resistance.

Entecavir is well tolerated. The most frequent adverse events are headache, fatigue, dizziness, and nausea. Lung adenomas and carcinomas in mice, hepatic adenomas and carcinomas in rats and mice, vascular tumors in mice, and brain gliomas and skin fibromas in rats have been observed at varying exposures. Co-administration of entecavir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the co-administered drug.

LAMIVUDINE

The pharmacokinetics of lamivudine are described earlier in this chapter (see section, Nucleoside and Nucleotide Reverse Transcriptase Inhibitors). The more prolonged intracellular half-life in HBV cell lines (17–19 hours) than in HIV-infected cell lines (10.5–15.5 hours) allows for lower doses and less frequent administration. Lamivudine can be safely administered to patients with decompensated liver disease.

Lamivudine inhibits HBV DNA polymerase and HIV reverse transcriptase by competing with deoxycytidine triphosphate for incorporation into the viral DNA, resulting in chain termination. Lamivudine achieves 3–4 log decreases in viral replication in most patients and suppression of HBV DNA to undetectable levels in about 44% of patients. Seroconversion of HBeAg from positive to

negative occurs in about 17% of patients and is durable at 3 years in about 70% of responders. Continuation of treatment for 4–8 months after seroconversion may improve the durability of response. Response in HBeAg-negative patients is initially high but less durable.

Although lamivudine initially results in rapid and potent virus suppression, chronic therapy may ultimately be limited by the emergence of lamivudine-resistant HBV isolates (eg, L180M or M204I/V), estimated to occur in 15–30% of patients at 1 year and 70% at 5 years of therapy. Resistance has been associated with flares of hepatitis and progressive liver disease. Cross-resistance between lamivudine and emtricitabine or entecavir may occur; however, adefovir maintains activity against lamivudine-resistant strains of HBV.

In the doses used for HBV infection, lamivudine has an excellent safety profile. Headache, nausea, and dizziness are rare. Co-infection with HIV may increase the risk of pancreatitis. No evidence of mitochondrial toxicity has been reported.

TELBIVUDINE

Telbivudine is a thymidine nucleoside analog with activity against HBV DNA polymerase. It is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. The phosphorylated compound competitively inhibits HBV DNA polymerase, resulting in incorporation into viral DNA and chain termination. It is not active in vitro against HIV-1.

Oral bioavailability is unaffected by food. Plasma protein-binding is low (3%) and distribution wide. The serum half-life is approximately 15 hours and excretion is renal. There are no known metabolites and no known interactions with the CYP450 system or other drugs.

In a comparative trial against lamivudine in patients with chronic HBV infection, significantly more patients receiving telbivudine achieved the combined end point of suppression of HBV DNA to less than 5 log copies/mL plus loss of serum HBeAg. The mean reduction in HBV DNA from baseline, the proportion with ALT normalization, and HBeAg seroconversion all were greater in those receiving telbivudine. Liver biopsies performed 1 year later showed less scarring. However, emergence of resistance, typically due to the M204I mutation, may occur in up to 22% of patients with durations of therapy exceeding 1 year, and may result in virologic rebound.

Adverse effects are mild; they include fatigue, headache, abdominal pain, upper respiratory infection, increased creatine kinase levels, and nausea and vomiting. Both uncomplicated myalgia and myopathy have been reported, as has peripheral neuropathy. As with other nucleoside analogs, lactic acidosis and severe hepatomegaly with steatosis may occur during therapy as well as flares of hepatitis after discontinuation.

TENOFOVIR

Tenofovir, a nucleotide analog of adenosine in use as an antiretroviral agent, has recently gained licensure for the treatment of patients with chronic HBV infection. The characteristics of tenofovir are described earlier in this chapter. Tenofovir maintains activity against lamivudine- and entecavir-resistant hepatitis virus isolates but has reduced activity against adefovir-resistant strains. Although similar in structure to adefovir dipivoxil, comparative trials showed a significantly higher rate of complete response, defined as serum HBV DNA levels less than 400 copies/mL, as well as of histologic improvement, in patients with chronic HBV infection receiving tenofovir than in those receiving adefovir dipivoxil. The emergence of resistance appears to be substantially less frequent during therapy with tenofovir than with adefovir.

INVESTIGATIONAL AGENTS

Compounds in clinical development for the treatment of patients with HBV infection include the nucleoside analogs **emtricitabine** and **clevudine,** as well as the immunologic modulator **thymosin alpha-1,** agents that facilitate uptake by the liver using conjugation to ligands, and RNA interference compounds.

TREATMENT OF HEPATITIS C INFECTION

In contrast to the treatment of patients with chronic HBV infection, the primary goal of treatment in patients with HCV infection is viral eradication. In clinical trials, the primary efficacy end point is typically achievement of sustained viral response (SVR), defined as the absence of detectable viremia for 6 months after completion of therapy. SVR is associated with improvement in liver histology, reduction in risk of hepatocellular carcinoma, and, occasionally, with regression of cirrhosis as well. Late relapse occurs in less than 5% of patients who achieve SVR.

In acute hepatitis C, the rate of clearance of the virus without therapy is estimated at 15–30%. In one (uncontrolled) study, treatment of acute infection with interferon alfa-2b, in doses higher than those used for chronic hepatitis C, resulted in a sustained rate of clearance of 95% at 6 months. Therefore, if HCV RNA testing documents persistent viremia 12 weeks after initial seroconversion, antiviral therapy is recommended.

Treatment of patients with chronic HCV infection is recommended for those with an increased risk for progression to cirrhosis. The parameters for selection are complex. In those who are to be treated, the current standard of treatment is once-weekly pegylated interferon alfa in combination with daily oral ribavirin. Pegylated interferon alfa-2a and -2b have replaced their unmodified interferon alfa counterparts because of superior efficacy in combination with ribavirin, regardless of genotype. It is also clear that combination therapy with oral ribavirin is more effective than monotherapy with either interferon or ribavirin alone. Therefore, monotherapy with pegylated interferon alfa is recommended only in patients who cannot tolerate ribavirin. Factors associated with a favorable therapeutic response include HCV genotype 2 or 3, absence of cirrhosis on liver biopsy, and low pretreatment HCV RNA levels.

RIBAVIRIN

Ribavirin is a guanosine analog that is phosphorylated intracellularly by host cell enzymes. Although its mechanism of action has not been fully elucidated, it appears to interfere with the synthesis of guanosine triphosphate, to inhibit capping of viral messenger RNA, and to inhibit the viral RNA-dependent polymerase of certain viruses. Ribavirin triphosphate inhibits the replication of a wide range of DNA and RNA viruses, including influenza A and B, parainfluenza, respiratory syncytial virus, paramyxoviruses, HCV, and HIV-1.

The absolute oral bioavailability of ribavirin is 45–64%, increases with high-fat meals, and decreases with co-administration of antacids. Plasma protein binding is negligible, volume of distribution is large, and cerebrospinal fluid levels are about 70% of those in plasma. Ribavirin elimination is primarily through the urine; therefore, clearance is decreased in patients with creatinine clearances less than 30 mL/min.

Higher doses of ribavirin (ie, 1000–1200 mg/d, according to weight, rather than 800 mg/d) or a longer duration of therapy or both may be more efficacious in those with a lower likelihood of response to therapy (eg, those with genotype 1 or 4) or in those who have relapsed. This must be balanced with an increased likelihood of toxicity. A dose-dependent hemolytic anemia occurs in 10–20% of patients. Other potential adverse effects are depression, fatigue, irritability, rash, cough, insomnia, nausea, and pruritus. Contraindications to ribavirin therapy include anemia, end-stage renal failure, ischemic vascular disease, and pregnancy. Ribavirin is teratogenic and embryotoxic in animals as well as mutagenic in mammalian cells. Patients exposed to the drug should not conceive children for at least 6 months thereafter.

NEW & INVESTIGATIONAL AGENTS

Among the agents for the treatment of HCV infection, those holding the greatest promise currently are the HCV NS3 protease inhibitors **telaprevir** and **boceprevir.** These highly potent agents are likely to decrease the overall duration of therapy, with possibly greater tolerability than current regimens. Another class of promising agents is the HCV NS5B polymerase inhibitors, including both nucleoside and nonnucleoside analogs.

■ ANTI-INFLUENZA AGENTS

Influenza virus strains are classified by their core proteins (ie, A, B, or C), species of origin (eg, avian, swine), and geographic site of isolation. Influenza A, the only strain that causes pandemics, is classified into 16 H (hemagglutinin) and 9 N (neuraminidase) known subtypes based on surface proteins. Although influenza B viruses usually infect only people, influenza A viruses can infect a variety of animal hosts. Current influenza A subtypes that are circulating among worldwide populations include H1N1, H1N2, and H3N2. Fifteen subtypes are known to infect birds, providing an extensive reservoir. Although avian influenza subtypes are typically highly species-specific, they have on rare occasions crossed the species barrier to infect humans and cats. Viruses of the H5 and H7 subtypes (eg, H5N1, H7N7, and H7N3) may rapidly mutate within poultry flocks from a low to high pathogenic form and have recently expanded their host range to cause both avian and human disease. Of particular concern is the avian H5N1 virus, which first caused human infection (including severe disease and death) in 1997 and has become endemic in Southeast Asian poultry since 2003. To date, the spread of H5N1 virus from person to person has been rare, limited, and unsustained. However, the emergence of the 2009 H1N1 influenza virus (previously called "swine flu") in 2009–2010 caused the first influenza pandemic (ie, global outbreak of disease caused by a new flu virus) in more than 40 years.

Although antiviral drugs available for influenza have activity against influenza A, many or most of the circulating strains of avian H5N1, as well as H1 and H3 strains causing seasonal influenza in the United States, are resistant to amantadine and rimantadine. Resistance to oseltamivir has also increased dramatically.

OSELTAMIVIR & ZANAMIVIR

The neuraminidase inhibitors oseltamivir and zanamivir, analogs of sialic acid, interfere with release of progeny influenza virus from infected host cells, thus halting the spread of infection within the respiratory tract. These agents competitively and reversibly interact with the active enzyme site to inhibit viral neuraminidase activity at low nanomolar concentrations. Inhibition of viral neuraminidase results in clumping of newly released influenza virions to each other and to the membrane of the infected cell. Unlike amantadine and rimantadine, oseltamivir and zanamivir have activity against both influenza A and influenza B viruses. Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness. When a 5-day course of therapy is initiated within 36–48 hours after the onset of symptoms, the duration of illness is decreased by 1–2 days compared with those on placebo, severity is diminished, and the incidence of secondary complications in children and adults decreases. Once-daily prophylaxis is 70–90% effective in preventing disease after exposure. Oseltamivir is approved by the Food and Drug Administration (FDA) for patients 1 year and older, whereas zanamivir is approved in patients 7 years or older.

Oseltamivir is an orally administered prodrug that is activated by hepatic esterases and widely distributed throughout the body. The dosage is 75 mg twice daily for 5 days for treatment and 75 mg once daily for prevention; dosage must be modified in patients with renal insufficiency. Oral bioavailability is approximately 80%, plasma protein binding is low, and concentrations in the middle ear and sinus fluid are similar to those in plasma. The half-life of oseltamivir is 6–10 hours, and excretion is by glomerular filtration and tubular secretion in the urine. Probenecid reduces renal clearance of oseltamivir by 50%. Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function; therefore, dosage should be

adjusted in such patients. Potential adverse effects include nausea, vomiting, and abdominal pain, which occur in 5–10% of patients early in therapy but tend to resolve spontaneously. Taking oseltamivir with food does not interfere with absorption and may decrease nausea and vomiting. Headache, fatigue, and diarrhea have also been reported and appear to be more common with prophylactic use. Rash is rare. Transient neuropsychiatric events (self-injury or delirium) have been reported, particularly in adolescents and adults living in Japan.

Zanamivir is delivered directly to the respiratory tract via inhalation. Ten to twenty percent of the active compound reaches the lungs, and the remainder is deposited in the oropharynx. The concentration of the drug in the respiratory tract is estimated to be more than 1000 times the 50% inhibitory concentration for neuraminidase, and the pulmonary half-life is 2.8 hours. Five to fifteen percent of the total dose (10 mg twice daily for 5 days for treatment and 10 mg once daily for prevention) is absorbed and excreted in the urine with minimal metabolism. Potential adverse effects include cough, bronchospasm (occasionally severe), reversible decrease in pulmonary function, and transient nasal and throat discomfort. Zanamivir administration is not recommended for patients with underlying airway disease.

Resistance to oseltamivir may be associated with point mutations in the viral hemagglutinin or neuraminidase (eg, the H275Y mutation) genes. Rates of resistance to oseltamivir among seasonal H1N1 viruses have risen abruptly and dramatically worldwide, reaching 97.4% in tested strains in the United States from 2008 to 2009. Resistance to oseltamivir in pandemic H1N1 viruses and resistance to zanamivir in seasonal and pandemic H1N1 viruses are rare. All influenza A (H3N2) and influenza B viruses were susceptible to both oseltamivir and zanamivir. Swine-origin influenza A (H1N1) viruses are nearly always susceptible to both oseltamivir and zanamivir.

AMANTADINE & RIMANTADINE

Amantadine (1-aminoadamantane hydrochloride) and its α-methyl derivative, rimantadine, are tricyclic amines of the adamantane family that block the M2 proton ion channel of the virus particle and inhibit uncoating of the viral RNA within infected host cells, thus preventing its replication. They are active against influenza A only. Rimantadine is four to ten times more active than amantadine in vitro. Amantadine is well absorbed and 67% protein-bound. Its plasma half-life is 12–18 hours and varies by creatinine clearance. Rimantadine is about 40% protein-bound and has a half-life of 24–36 hours. Nasal secretion and salivary levels approximate those in the serum, and cerebrospinal fluid levels are 52–96% of those in the serum; nasal mucus concentrations of rimantadine average 50% higher than those in plasma. Amantadine is excreted unchanged in the urine, whereas rimantadine undergoes extensive metabolism by hydroxylation, conjugation, and glucuronidation before urinary excretion. Dose reductions are required for both agents in the elderly and in patients with renal insufficiency, and for rimantadine in patients with marked hepatic insufficiency.

In the absence of resistance, both amantadine and rimantadine, at 100 mg twice daily or 200 mg once daily, are 70–90% protective in the prevention of clinical illness when initiated before exposure. When begun within 1–2 days after the onset of illness, the duration of fever and systemic symptoms is reduced by 1–2 days.

The primary target for both agents is the M2 protein within the viral membrane, incurring both influenza A specificity and a mutation-prone site that results in the rapid development of resistance in up to 50% of treated individuals. Resistant isolates with single-point mutations are genetically stable, retain pathogenicity, can be transmitted to close contacts, and may be shed chronically by immunocompromised patients. The marked increase in the prevalence of resistance to both agents in clinical isolates over the last decade, in influenza A H1N1 as well as H3N2, has limited the usefulness of these agents for either the treatment or the prevention of influenza. Cross-resistance to zanamivir and oseltamivir does not occur.

The most common adverse effects are gastrointestinal (nausea, anorexia) and central nervous system (nervousness, difficulty in concentrating, insomnia, light-headedness); side effects are dose-related and may diminish or disappear after the first week of treatment despite continued drug ingestion. More serious side effects (eg, marked behavioral changes, delirium, hallucinations, agitation, and seizures) may be due to alteration of dopamine neurotransmission (see Chapter 28); are less frequent with rimantadine than with amantadine; are associated with high plasma concentrations; may occur more frequently in patients with renal insufficiency, seizure disorders, or advanced age; and may increase with concomitant antihistamines, anticholinergic drugs, hydrochlorothiazide, and trimethoprim-sulfamethoxazole. Clinical manifestations of anticholinergic activity tend to be present in acute amantadine overdose. Both agents are teratogenic and embryotoxic in rodents, and birth defects have been reported after exposure during pregnancy.

INVESTIGATIONAL AGENTS

The neuraminidase inhibitor **peramivir,** a cyclopentane analog, has activity against both influenza A and B viruses. Peramivir received temporary emergency use authorization by FDA for intravenous administration in November 2009 due to the H1N1 pandemic. The drug is marketed in South Korea but has not yet been licensed in the United States. Clinical data on cross-resistance to oseltamivir and zanamivir are not yet available. Reported side effects include diarrhea, nausea, vomiting, and neutropenia.

OTHER ANTIVIRAL AGENTS

INTERFERONS

Interferons have been studied for numerous clinical indications. In addition to HBV and HCV infections (see Antihepatitis Agents), intralesional injection of interferon alfa-2b or alfa-n3 may be used for treatment of condylomata acuminata (see Chapter 61).

RIBAVIRIN

In addition to oral administration for HCV infection in combination with interferon alfa (see Antihepatitis Agents), aerosolized ribavirin is administered by nebulizer (20 mg/mL for 12–18 hours per day) to children and infants with severe respiratory syncytial virus (RSV) bronchiolitis or pneumonia to reduce the severity and duration of illness. Aerosolized ribavirin has also been used to treat influenza A and B infections but has not gained widespread use. Systemic absorption is low (< 1%). Aerosolized ribavirin is generally well tolerated but may cause conjunctival or bronchial irritation. Health care workers should be protected against extended inhalation exposure. The aerosolized drug may precipitate on contact lenses.

Intravenous ribavirin decreases mortality in patients with Lassa fever and other viral hemorrhagic fevers if started early. High concentrations inhibit West Nile virus in vitro, but clinical data are lacking. Clinical benefit has been reported in cases of severe measles pneumonitis and certain encephalitides, and continuous infusion of ribavirin has decreased virus shedding in several patients with severe lower respiratory tract influenza or parainfluenza infections. At steady state, cerebrospinal fluid levels are about 70% of those in plasma.

PALIVIZUMAB

Palivizumab is a humanized monoclonal antibody directed against an epitope in the A antigen site on the F surface protein of RSV. It is licensed for the prevention of RSV infection in high-risk infants and children, such as premature infants and those with bronchopulmonary dysplasia or congenital heart disease. A placebo-controlled trial using once-monthly intramuscular injections (15 mg/kg) for 5 months beginning at the start of the RSV season demonstrated a 55% reduction in the risk of hospitalization for RSV in treated patients, as well as decreases in the need for supplemental oxygen, the illness severity score, and the need for intensive care. Although resistant strains have been isolated in the laboratory, no resistant clinical isolates have yet been identified. Potential adverse effects include upper respiratory tract infection, fever, rhinitis, rash, diarrhea, vomiting, cough, otitis media, and elevation in serum aminotransferase levels.

A number of other agents are under investigation for the treatment or prophylaxis of patients with RSV infection, including the RNA interference (RNAi) therapeutic ALN-RSV01, the humanized monoclonal antibody motavizumab, and the benzodiazepine RSV604.

IMIQUIMOD

Imiquimod is an immune response modifier shown to be effective in the topical treatment of external genital and perianal warts (ie, condyloma acuminatum; see Chapter 61). The 5% cream is applied three times weekly and washed off 6–10 hours after each application. Recurrences appear to be less common than after ablative therapies. Imiquimod may also be effective against molluscum contagiosum but is not licensed in the United States for this indication. Local skin reactions are the most common adverse effect; these tend to resolve within weeks after therapy. However, pigmentary skin changes may persist. Systemic adverse effects such as fatigue and influenza-like syndrome have occasionally been reported.

PREPARATIONS AVAILABLE

Abacavir
Oral (Ziagen): 300 mg tablets; 20 mg/mL solution
Oral (Epzicom): 600 mg plus 300 mg lamivudine
Oral (Trizivir): 300 mg tablets in combination with 150 mg lamivudine and 300 mg zidovudine

Acyclovir (generic, Zovirax)
Oral: 200 mg capsules; 400, 800 mg tablets; 200 mg/5 mL suspension
Parenteral: 50 mg/mL; powder to reconstitute for injection (500, 1000 mg/vial)
Topical: 5% ointment

Adefovir (Hepsera)
Oral: 10 mg tablets

Amantadine (generic, Symmetrel)
Oral: 100 mg capsules, tablets; 50 mg/5 mL syrup

Atazanavir (Reyataz)
Oral: 100, 150, 200 mg capsules

Boceprivir (Victrelis)
Oral: 375 mg tablets

Cidofovir (Vistide)
Parenteral: 375 mg/vial (75 mg/mL) for IV injection

Darunavir (Prezista)
Oral: 300 mg tablets (must be taken with ritonavir)

Delavirdine (Rescriptor)
Oral: 100, 200 mg tablets

Didanosine (dideoxyinosine, ddI)
Oral (Videx): 25, 50, 100, 150, 200 mg tablets; 100, 167, 250 mg powder for oral solution; 2, 4 g powder for pediatric solution
Oral (Videx-EC): 125, 200, 250, 400 mg delayed-release capsules

Docosanol (Abreva) (over-the-counter)
Topical: 10% cream

Efavirenz (Sustiva)
Oral: 50, 100, 200 mg capsules; 600 mg tablets

Emtricitabine
Oral (Emtriva): 200 mg tablets
Oral (Truvada): 200 mg plus 300 mg tenofovir tablets
Oral (Atripla): 200 mg plus 300 mg tenofovir plus 600 mg efavirenz

Enfuvirtide (Fuzeon)
Parenteral: 90 mg/mL for injection

Entecavir (Baraclude)
Oral: 0.5, 1 mg tablets; 0.05 mg/mL oral solution

Etravirine (Intelence)
Oral: 100 mg tablets

Famciclovir (Famvir)
Oral: 125, 250, 500 mg tablets

Fosamprenavir (Lexiva)
Oral: 700 mg tablets

Foscarnet (Foscavir)
Parenteral: 24 mg/mL for IV injection

Ganciclovir (Cytovene)
Oral: 250, 500 mg capsules
Parenteral: 500 mg/vial for IV injection
Intraocular implant (Vitrasert): 4.5 mg ganciclovir/implant

Imiquimod (Aldara)
Topical: 5% cream

Indinavir (Crixivan)
Oral: 100, 200, 333, 400 mg capsules

Interferon alfa-2a (Roferon-A)
Parenteral: 3, 6, 9, 36 million IU vials

Interferon alfa-2b (Intron A)
Parenteral: 3, 5, 10, 18, 25, and 50 million IU vials

Interferon alfa-2b (Rebetron)
Parenteral: 3 million IU vials (supplied with oral ribavirin, 200 mg capsules)

Interferon alfa-n3 (Alferon N)
Parenteral: 5 million IU/vial

Interferon alfacon-1 (Infergen)
Parenteral: 9 and 15 mcg vials

Lamivudine
Oral (Epivir): 150, 300 mg tablets; 10 mg/mL oral solution
Oral (Epivir-HBV): 100 mg tablets; 5 mg/mL solution
Oral (Combivir): 150 mg tablets in combination with 300 mg zidovudine
Oral (Trizivir): 150 mg tablets in combination with 300 mg abacavir and 300 mg zidovudine

Lopinavir/ritonavir (Kaletra)
Oral: 133.3 mg/33.3 mg capsules; 80 mg/20 mg per mL solution

Maraviroc (Selzentry)
Oral: 150, 300 mg tablets

Nelfinavir (Viracept)
Oral: 250, 625 mg tablets; 50 mg/g powder

Nevirapine (Viramune)
Oral: 200 mg tablets; 50 mg/5 mL suspension

Oseltamivir (Tamiflu)
Oral: 75 mg capsules; powder to reconstitute as suspension (12 mg/mL)

Palivizumab (Synagis)
Parenteral: 50, 100 mg/vial

Peginterferon alfa-2a (pegylated interferon alfa-2a, Pegasys)
Parenteral: 180 mcg/mL

Peginterferon alfa-2b (pegylated interferon alfa-2b, PEG-Intron)
Parenteral: powder to reconstitute as 100, 160, 240, 300 mcg/mL injection

Penciclovir (Denavir)
Topical: 1% cream

Raltegravir (Isentress)
Oral: 400 mg tablets

Ribavirin
Aerosol (Virazole): powder to reconstitute for aerosol; 6 g/100 mL vial
Oral (Rebetol, generic): 200 mg capsules, tablets; 40 mg/mL oral solution
Oral (Rebetron): 200 mg in combination with 3 million units interferon alfa-2b (Intron-A)

Rilpivirine
Oral (Edurant): 25 mg tablets
Oral (Complera): 200 mg emtricitabine, 25 mg rilpivirine, 300 mg tenofovir) tablets

Rimantadine (Flumadine)
Oral: 100 mg tablets; 50 mg/5 mL syrup

Ritonavir (Norvir)
Oral: 100 mg capsules; 80 mg/mL oral solution

Saquinavir
Oral (Invirase): 200 mg hard gel capsules, 500 mg tablets

Stavudine
Oral (Zerit): 15, 20, 30, 40 mg capsules; powder for 1 mg/mL oral solution
Oral extended-release (Zerit XR): 37.5, 50, 75, 100 mg capsules

Telaprivir (Incivik)
Oral: 200 mg capsules

Telbivudine (Tyzeka)
Oral: 600 mg tablets

Tenofovir (Viread)
Oral: 300 mg tablets

Tipranavir (Aptivus)
Oral: 250 mg capsules

Trifluridine (Viroptic)
Topical: 1% ophthalmic solution

Valacyclovir (Valtrex)
Oral: 500, 1000 mg tablets

Valganciclovir (Valcyte)
Oral: 450 mg capsules

Zalcitabine (dideoxycytidine, ddC) (Hivid)
Oral: 0.375, 0.75 mg tablets

Zanamivir (Relenza)
Inhalational: 5 mg/blister

Zidovudine (azidothymidine, AZT) (Retrovir)
Oral: 100 mg capsules, 300 mg tablets, 50 mg/5 mL syrup
Oral (Combivir): 300 mg tablets in combination with 150 mg lamivudine
Oral (Trizivir): 300 mg tablets in combination with 150 mg lamivudine and 300 mg zidovudine
Parenteral: 10 mg/mL

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RELEVANT WEB SITES

http://www.aidsinfo.nih.gov

http://www.hiv-druginteractions.org

http://www.hivinsite.com

http://www.iasusa.org

CASE STUDY ANSWER

Combination antiviral therapy against both HIV and hepatitis B virus (HBV) is indicated in this patient, given the high viral load and low CD4 cell count. However, the use of methadone and possibly excessive alcohol consumption necessitate caution. Tenofovir and emtricitabine (two nucleoside/nucleotide reverse transcriptase inhibitors) would be a potentially excellent choice as components of an initial regimen, since both are active against HIV-1 and HBV, do not interact with methadone, and are available in a once-daily, fixed-dose combination. Efavirenz, a nonnucleoside reverse transcriptase inhibitor, could be added and still maintain a once-daily regimen. Prior to initiation of this regimen, renal function should be checked, and a bone mineral density test should be considered. Pregnancy should be ruled out, and the patient should be counseled that efavirenz should not be taken during pregnancy. The potential for lowered methadone levels with efavirenz necessitates close monitoring and possibly an increased dose of methadone.

CHAPTER

50

Miscellaneous Antimicrobial Agents; Disinfectants, Antiseptics, & Sterilants

Daniel H. Deck, PharmD, & Lisa G. Winston, MD*

CASE STUDY

A 66-year-old man is admitted to the intensive care unit of a hospital for treatment of community-acquired pneumonia. He receives ceftriaxone and azithromycin upon admission, rapidly improves, and is transferred to a semiprivate ward room. On day 7 of his hospitalization, he develops copious diarrhea with eight bowel movements that day but is otherwise clinically stable. *Clostridium difficile*-associated colitis is suspected and a toxin assay is sent to confirm this diagnosis. What is an acceptable treatment for the patient's diarrhea? The patient is transferred to a single-bed room the following day. The housekeeping staff asks if the old room should be cleaned with alcohol or bleach. Which product should be chosen? Why?

METRONIDAZOLE, MUPIROCIN, POLYMYXINS, & URINARY ANTISEPTICS

METRONIDAZOLE

Metronidazole is a nitroimidazole antiprotozoal drug (see Chapter 52) that also has potent antibacterial activity against anaerobes, including *Bacteroides* and *Clostridium* species. Metronidazole is selectively absorbed by anaerobic bacteria and sensitive protozoa. Once taken up by anaerobes, it is nonenzymatically reduced by reacting with reduced ferredoxin. This reduction results in products that are toxic to anaerobic cells, and allows for their selective accumulation in anaerobes. The metabolites of metronidazole are taken up into bacterial DNA, forming unstable molecules. This action only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect on human cells or aerobic bacteria.

Metronidazole is well absorbed after oral administration, is widely distributed in tissues, and reaches serum levels of 4–6 mcg/mL after a 250-mg oral dose. It can also be given intravenously or by rectal suppository. The drug penetrates well into the cerebrospinal fluid and brain, reaching levels similar to those in serum. Metronidazole is metabolized in the liver and may accumulate in hepatic insufficiency.

Metronidazole is indicated for treatment of anaerobic or mixed intra-abdominal infections (in combination with other agents with activity against aerobic organisms), vaginitis (trichomonas infection, bacterial vaginosis), *Clostridium difficile* colitis, and brain abscess. The typical dosage is 500 mg three times daily orally or intravenously (30 mg/kg/d). Vaginitis may respond to a single 2 g dose. A vaginal gel is available for topical use.

Adverse effects include nausea, diarrhea, stomatitis, and peripheral neuropathy with prolonged use. Metronidazole has a disulfiram-like effect, and patients should be instructed to avoid

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alcohol. Although teratogenic in some animals, metronidazole has not been associated with this effect in humans. Other properties of metronidazole are discussed in Chapter 52.

A structurally similar agent, **tinidazole,** is a once-daily drug approved for treatment of trichomonas infection, giardiasis, and amebiasis. It also is active against anaerobic bacteria, but is not approved by the Food and Drug Administration (FDA) for treatment of anaerobic infections.

MUPIROCIN

Mupirocin (pseudomonic acid) is a natural substance produced by *Pseudomonas fluorescens.* It is rapidly inactivated after absorption, and systemic levels are undetectable. It is available as an ointment for topical application.

Mupirocin is active against gram-positive cocci, including methicillin-susceptible and methicillin-resistant strains of *Staphylococcus aureus.* Mupirocin inhibits staphylococcal isoleucyl tRNA synthetase. Low-level resistance, defined as a minimum inhibitory concentration (MIC) of up to 100 mcg/mL, is due to point mutation in the gene of the target enzyme. Low-level resistance has been observed after prolonged use. However, local concentrations achieved with topical application are well above this MIC, and this level of resistance does not lead to clinical failure. High-level resistance, with MICs exceeding 1000 mcg/mL, is due to the presence of a second isoleucyl tRNA synthetase gene, which is plasmid-encoded. High-level resistance results in complete loss of activity. Strains with high-level resistance have caused hospital-associated (nosocomial) outbreaks of staphylococcal infection and colonization. Although higher rates of resistance are encountered with intensive use of mupirocin, more than 95% of staphylococcal isolates are still susceptible.

Mupirocin is indicated for topical treatment of minor skin infections, such as impetigo (see Chapter 61). Topical application over large infected areas, such as decubitus ulcers or open surgical wounds, is an important factor leading to emergence of mupirocin-resistant strains and is not recommended. Mupirocin effectively eliminates *S aureus* nasal carriage by patients or health care workers, but results are mixed with respect to its ability to prevent subsequent staphylococcal infection.

POLYMYXINS

The polymyxins are a group of basic peptides active against gram-negative bacteria and include **polymyxin B** and **polymyxin E (colistin)**. Polymyxins act as cationic detergents. They attach to and disrupt bacterial cell membranes. They also bind and inactivate endotoxin. Gram-positive organisms, *Proteus* sp, and *Neisseria* sp are resistant.

Owing to their significant toxicity with systemic administration, polymyxins are largely restricted to topical use. Ointments containing polymyxin B, 0.5 mg/g, in mixtures with bacitracin or neomycin (or both) are commonly applied to infected superficial skin lesions. Emergence of strains of *Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacteriaceae that are resistant to all other agents has renewed interest in polymyxins as a parenteral agents for salvage therapy of infections caused by these organisms.

FIDAXOMICIN

Fidaxomicin is a narrow-spectrum, macrocyclic antibiotic that is active against gram-positive aerobes and anaerobes but lacks activity against gram-negative bacteria. Fidaxomicin inhibits bacterial protein synthesis by binding to the sigma subunit of RNA polymerase. When administered orally, systemic absorption is negligible but fecal concentrations are high. Fidaxomicin has been approved by the FDA for the treatment for *C difficile* colitis in adults. Preliminary data have demonstrated it is as effective as oral vancomycin and may be associated with lower rates of relapsing disease. The FDA has granted orphan drug designation to all formulations of fidaxomicin for the treatment of *C difficile* infection in pediatric patients aged 16 years and younger. Fidaxomicin is administered as 200 mg orally twice daily.

URINARY ANTISEPTICS

Urinary antiseptics are oral agents that exert antibacterial activity in the urine but have little or no systemic antibacterial effect. Their usefulness is limited to lower urinary tract infections. Prolonged suppression of bacteriuria with urinary antiseptics may be desirable in chronic or recurrent urinary tract infections in which eradication of infection by short-term systemic therapy has not been possible.

Nitrofurantoin

At therapeutic doses, **nitrofurantoin** is bactericidal for many gram-positive and gram-negative bacteria; however, *P aeruginosa* and many strains of *Proteus* are inherently resistant. Nitrofurantoin has a complex mechanism of action that is not fully understood. Antibacterial activity appears to correlate with rapid intracellular conversion of nitrofurantoin to highly reactive intermediates by bacterial reductases. These intermediates react nonspecifically with many ribosomal proteins and disrupt the synthesis of proteins, RNA, DNA, and metabolic processes. It is not known which of the multiple actions of nitrofurantoin is primarily responsible for its bactericidal activity.

There is no cross-resistance between nitrofurantoin and other antimicrobial agents, and resistance emerges slowly. As resistance to trimethoprim-sulfamethoxazole and fluoroquinolones has become more common in *Escherichia coli*, nitrofurantoin has become an important alternative oral agent for treatment of uncomplicated urinary tract infection.

Nitrofurantoin is well absorbed after ingestion. It is metabolized and excreted so rapidly that no systemic antibacterial action is achieved. The drug is excreted into the urine by both glomerular

filtration and tubular secretion. With average daily doses, concentrations of 200 mcg/mL are reached in urine. In renal failure, urine levels are insufficient for antibacterial action, but high blood levels may cause toxicity. Nitrofurantoin is contraindicated in patients with significant renal insufficiency (creatinine clearance < 60 mL/min).

The dosage for urinary tract infection in adults is 100 mg orally taken four times daily. The drug should not be used to treat upper urinary tract infection. Oral nitrofurantoin can be given for months for the suppression of chronic urinary tract infection. It is desirable to keep urinary pH below 5.5, which greatly enhances drug activity. A single daily dose of nitrofurantoin, 100 mg, can prevent recurrent urinary tract infections in some women.

Anorexia, nausea, and vomiting are the principal side effects of nitrofurantoin. Neuropathies and hemolytic anemia occur in patients with glucose-6-phosphate dehydrogenase deficiency. Nitrofurantoin antagonizes the action of nalidixic acid. Rashes, pulmonary infiltration and fibrosis, and other hypersensitivity reactions have been reported.

Methenamine Mandelate & Methenamine Hippurate

Methenamine mandelate is the salt of mandelic acid and methenamine and possesses properties of both of these urinary antiseptics. Methenamine hippurate is the salt of hippuric acid and methenamine. Below pH 5.5, methenamine releases formaldehyde, which is antibacterial (see Aldehydes, below). Mandelic acid or hippuric acid taken orally is excreted unchanged in the urine, in which these drugs are bactericidal for some gram-negative bacteria when pH is less than 5.5.

Methenamine mandelate, 1 g four times daily, or methenamine hippurate, 1 g twice daily by mouth (children, 50 mg/kg/d or 30 mg/kg/d, respectively), is used only as a urinary antiseptic to suppress, not treat, urinary tract infection. Acidifying agents (eg, ascorbic acid, 4–12 g/d) may be given to lower urinary pH below 5.5. Sulfonamides should not be given at the same time because they may form an insoluble compound with the formaldehyde released by methenamine. Persons taking methenamine mandelate may exhibit falsely elevated tests for catecholamine metabolites.

■ DISINFECTANTS, ANTISEPTICS, & STERILANTS

Disinfectants are strong chemical agents that inhibit or kill microorganisms (Table 50–1). Antiseptics are disinfecting agents with sufficiently low toxicity for host cells that they can be used directly on skin, mucous membranes, or wounds. Sterilants kill both vegetative cells and spores when applied to materials for appropriate times and temperatures. Some of the terms used in this context are defined in Table 50–2.

Disinfection prevents infection by reducing the number of potentially infective organisms by killing, removing, or diluting them. Disinfection can be accomplished by application of chemical agents or use of physical agents such as ionizing radiation, dry or moist heat, or superheated steam (autoclave, 120°C) to kill microorganisms. Often a combination of agents is used, eg, water and moderate heat over time (pasteurization); ethylene oxide and moist heat (a sterilant); or addition of disinfectant to a detergent. Prevention of infection also can be achieved by washing, which dilutes the potentially infectious organism, or by establishing a

TABLE 50–1 Activities of disinfectants.

	Bacteria			Viruses			Other		
	Gram-Positive	*Gram-Negative*	*Acid-Fast*	*Spores*	*Lipophilic*	*Hydrophilic*	*Fungi*	*Amebic Cysts*	*Prions*
Alcohols (isopropanol, ethanol)	HS	HS	S	R	S	V	…	…	R
Aldehydes (glutaraldehyde, formaldehyde)	HS	HS	MS	S (slow)	S	MS	S	…	R
Chlorhexidine gluconate	HS	MS	R	R	V	R	…	…	R
Sodium hypochlorite, chlorine dioxide	HS	HS	MS	S (pH 7.6)	S	S (at high conc)	MS	S	MS (at high conc)
Hexachlorophene	S (slow)	R	R	R	R	R	R	R	R
Povidone, iodine	HS	HS	S	S (at high conc)	S	R	S	S	R
Phenols, quaternary ammonium compounds	HS	HS	MS	R	S	R	S	…	R

HS, highly susceptible; S, susceptible; MS, moderately susceptible; R, resistant; V, variable; …, no data.

TABLE 50–2 Commonly used terms related to chemical and physical killing of microorganisms.

Antisepsis	Application of an agent to living tissue for the purpose of preventing infection
Decontamination	Destruction or marked reduction in number or activity of microorganisms
Disinfection	Chemical or physical treatment that destroys most vegetative microbes or viruses, but not spores, in or on inanimate surfaces
Sanitization	Reduction of microbial load on an inanimate surface to a level considered acceptable for public health purposes
Sterilization	A process intended to kill or remove all types of microorganisms, including spores, and usually including viruses, with an acceptably low probability of survival
Pasteurization	A process that kills nonsporulating microorganisms by hot water or steam at 65–100°C

barrier, eg, gloves, condom, or respirator, which prevents the pathogen from gaining entry to the host.

Hand hygiene is the most important means of preventing transmission of infectious agents from person to person or from regions of high microbial load, eg, mouth, nose, or gut, to potential sites of infection. Soap and warm water efficiently and effectively remove bacteria. Skin disinfectants along with detergent and water are usually used preoperatively as a surgical scrub for surgeons' hands and the patient's surgical incision.

Evaluation of effectiveness of antiseptics, disinfectants, and sterilants, although seemingly simple in principle, is very complex. Factors in any evaluation include the intrinsic resistance of the microorganism, the number of microorganisms present, mixed populations of organisms, amount of organic material present (eg, blood, feces, tissue), concentration and stability of disinfectant or sterilant, time and temperature of exposure, pH, and hydration and binding of the agent to surfaces. Specific, standardized assays of activity are defined for each use. Toxicity for humans also must be evaluated. In the United States, the Environmental Protection Agency (EPA) regulates disinfectants and sterilants and the FDA regulates antiseptics.

Users of antiseptics, disinfectants, and sterilants need to consider their short-term and long-term toxicity because they may have general biocidal activity and may accumulate in the environment or in the body of the patient or caregiver using the agent. Disinfectants and antiseptics may also become contaminated by resistant microorganisms—eg, spores, *P aeruginosa*, or *Serratia marcescens*—and actually transmit infection. Most topical antiseptics interfere with wound healing to some degree. Simple cleansing of wounds with soap and water is less damaging than the application of antiseptics. Topical antibiotics with a narrow spectrum of action and low toxicity (eg, bacitracin and mupirocin) can be used for temporary control of bacterial growth and are generally preferred to antiseptics. Methenamine-containing agents release formaldehyde in a low antibacterial concentration at acid pH and can be an effective urinary antiseptic for long-term control of urinary tract infections.

Some of the chemical classes of antiseptics, disinfectants, and sterilants are described briefly in the text that follows. The reader is referred to the general references for descriptions of physical disinfection and sterilization methods.

ALCOHOLS

The two alcohols most frequently used for antisepsis and disinfection are **ethanol** and **isopropyl alcohol (isopropanol)**. They are rapidly active, killing vegetative bacteria, *Mycobacterium tuberculosis*, and many fungi, and inactivating lipophilic viruses. The optimum bactericidal concentration is 60–90% by volume in water. They probably act by denaturation of proteins. They are not used as sterilants because they are not sporicidal, do not penetrate protein-containing organic material, may not be active against hydrophilic viruses, and lack residual action because they evaporate completely. The alcohols are useful in situations in which sinks with running water are not available for washing with soap and water. Their skin-drying effect can be partially alleviated by addition of emollients to the formulation. Use of alcohol-based hand rubs has been shown to reduce transmission of health care-associated bacterial pathogens and is recommended by the Centers for Disease Control and Prevention (CDC) as the preferred method of hand decontamination. Alcohol-based hand rubs are ineffective against spores of *C difficile,* and assiduous handwashing with soap and water is still required for decontamination after caring for a patient with infection from this organism.

Alcohols are flammable and must be stored in cool, well-ventilated areas. They must be allowed to evaporate before cautery, electrosurgery, or laser surgery. Alcohols may be damaging if applied directly to corneal tissue. Therefore, instruments such as tonometers that have been disinfected in alcohol should be rinsed with sterile water, or the alcohol should be allowed to evaporate before they are used.

CHLORHEXIDINE

Chlorhexidine is a cationic biguanide with very low water solubility. Water-soluble chlorhexidine digluconate is used in water-based formulations as an antiseptic. It is active against vegetative bacteria and mycobacteria and has moderate activity against fungi and viruses. It strongly adsorbs to bacterial membranes, causing leakage of small molecules and precipitation of cytoplasmic proteins. It is active at pH 5.5–7.0. Chlorhexidine gluconate is slower in its action than alcohols, but, because of its persistence, it has residual activity when used repeatedly, producing bactericidal action equivalent to alcohols. It is most effective against gram-positive cocci and less active against gram-positive and gram-negative rods. Spore germination is inhibited by chlorhexidine. Chlorhexidine digluconate is resistant to inhibition by blood and organic materials. However, anionic and nonionic agents in

moisturizers, neutral soaps, and surfactants may neutralize its action. Chlorhexidine digluconate formulations of 4% concentration have slightly greater antibacterial activity than newer 2% formulations. The combination of chlorhexidine gluconate in 70% alcohol, available in some countries including the United States, is the preferred agent for skin antisepsis in many surgical and percutaneous procedures. The advantage of this combination over povidone-iodine may derive from its more rapid action after application, its retained activity after exposure to body fluids, and its persistent activity on the skin. Chlorhexidine has a very low skin-sensitizing or irritating capacity. Oral toxicity is low because it is poorly absorbed from the alimentary tract. Chlorhexidine must not be used during surgery on the middle ear because it causes sensorineural deafness. Similar neural toxicity may be encountered during neurosurgery.

HALOGENS

Iodine

Iodine in a 1:20,000 solution is bactericidal in 1 minute and kills spores in 15 minutes. Tincture of iodine USP contains 2% iodine and 2.4% sodium iodide in alcohol. It is the most active antiseptic for intact skin. It is not commonly used because of serious hypersensitivity reactions that may occur and because of its staining of clothing and dressings.

Iodophors

Iodophors are complexes of iodine with a surface-active agent such as **polyvinyl pyrrolidone (PVP; povidone-iodine).** Iodophors retain the activity of iodine. They kill vegetative bacteria, mycobacteria, fungi, and lipid-containing viruses. They may be sporicidal upon prolonged exposure. Iodophors can be used as antiseptics or disinfectants, the latter containing more iodine. The amount of free iodine is low, but it is released as the solution is diluted. An iodophor solution must be diluted according to the manufacturer's directions to obtain full activity.

Iodophors are less irritating and less likely to produce skin hypersensitivity than tincture of iodine. They require drying time on skin before becoming active, which can be a disadvantage. Although iodophors have a somewhat broader spectrum of activity than chlorhexidine, including sporicidal action, they lack its persistent activity on skin.

Chlorine

Chlorine is a strong oxidizing agent and universal disinfectant that is most commonly provided as a 5.25% **sodium hypochlorite** solution, a typical formulation for **household bleach.** Because formulations may vary, the exact concentration should be verified on the label. A 1:10 dilution of household bleach provides 5000 ppm of available chlorine. The CDC recommends this concentration for disinfection of blood spills. Less than 5 ppm kills vegetative bacteria, whereas up to 5000 ppm is necessary to kill spores. A concentration of 1000–10,000 ppm is tuberculocidal. One hundred ppm kills vegetative fungal cells in 1 hour, but fungal spores require 500 ppm. Viruses are inactivated by 200–500 ppm. Dilutions of 5.25% sodium hypochlorite made up in pH 7.5–8.0 tap water retain their activity for months when kept in tightly closed, opaque containers. Frequent opening and closing of the container reduces the activity markedly.

Because chlorine is inactivated by blood, serum, feces, and protein-containing materials, surfaces should be cleaned before chlorine disinfectant is applied. Undissociated hypochlorous acid (HOCl) is the active biocidal agent. When pH is increased, the less active hypochlorite ion, OCl^-, is formed. When hypochlorite solutions contact formaldehyde, the carcinogen bischloromethyl is formed. Rapid evolution of irritating chlorine gas occurs when hypochlorite solutions are mixed with acid and urine. Solutions are corrosive to aluminum, silver, and stainless steel.

Alternative chlorine-releasing compounds include **chlorine dioxide** and **chloramine T.** These agents retain chlorine longer and have a prolonged bactericidal action.

PHENOLICS

Phenol itself (perhaps the oldest of the surgical antiseptics) is no longer used even as a disinfectant because of its corrosive effect on tissues, its toxicity when absorbed, and its carcinogenic effect. These adverse actions are diminished by forming derivatives in which a functional group replaces a hydrogen atom in the aromatic ring. The phenolic agents most commonly used are ***o*-phenylphenol, *o*-benzyl-*p*-chlorophenol,** and ***p*-tertiary amylphenol.** Mixtures of phenolic derivatives are often used. Some of these are derived from coal tar distillates, eg, cresols and xylenols. Skin absorption and skin irritation still occur with these derivatives, and appropriate care is necessary in their use. Detergents are often added to formulations to clean and remove organic material that may decrease the activity of a phenolic compound.

Phenolic compounds disrupt cell walls and membranes, precipitate proteins, and inactivate enzymes. They are bactericidal (including mycobacteria) and fungicidal and are capable of inactivating lipophilic viruses. They are not sporicidal. Dilution and time of exposure recommendations of the manufacturer must be followed.

Phenolic disinfectants are used for hard surface decontamination in hospitals and laboratories, eg, floors, beds, and counter or bench tops. They are not recommended for use in nurseries and especially in bassinets, where their use has been associated with hyperbilirubinemia. Use of **hexachlorophene** as a skin disinfectant has caused cerebral edema and convulsions in premature infants and, occasionally, in adults.

QUATERNARY AMMONIUM COMPOUNDS

The quaternary ammonium compounds ("quats") are cationic surface-active detergents. The active cation has at least one long water-repellent hydrocarbon chain, which causes the molecules to

concentrate as an oriented layer on the surface of solutions and colloidal or suspended particles. The charged nitrogen portion of the cation has high affinity for water and prevents separation out of solution. The bactericidal action of quaternary compounds has been attributed to inactivation of energy-producing enzymes, denaturation of proteins, and disruption of the cell membrane. These agents are fungistatic and sporistatic and also inhibit algae. They are bactericidal for gram-positive bacteria and moderately active against gram-negative bacteria. Lipophilic viruses are inactivated. They are not tuberculocidal or sporicidal, and they do not inactivate hydrophilic viruses. Quaternary ammonium compounds bind to the surface of colloidal protein in blood, serum, and milk and to the fibers in cotton, mops, cloths, and paper towels used to apply them, which can cause inactivation of the agent by removing it from solution. They are inactivated by anionic detergents (soaps), by many nonionic detergents, and by calcium, magnesium, ferric, and aluminum ions.

Quaternary compounds are used for sanitation of noncritical surfaces (floors, bench tops, etc). Their low toxicity has led to their use as sanitizers in food production facilities. The CDC recommends that quaternary ammonium compounds such as **benzalkonium chloride** *not* be used as antiseptics because several outbreaks of infections have occurred that were due to growth of *Pseudomonas* and other gram-negative bacteria in quaternary ammonium antiseptic solutions.

ALDEHYDES

Formaldehyde and **glutaraldehyde** are used for disinfection or sterilization of instruments such as fiberoptic endoscopes, respiratory therapy equipment, hemodialyzers, and dental handpieces that cannot withstand exposure to the high temperatures of steam sterilization. They are not corrosive for metal, plastic, or rubber. These agents have a broad spectrum of activity against microorganisms and viruses. They act by alkylation of chemical groups in proteins and nucleic acids. Failures of disinfection or sterilization can occur as a result of dilution below the known effective concentration, the presence of organic material, and the failure of liquid to penetrate into small channels in the instruments. Automatic circulating baths are available that increase penetration of aldehyde solution into the instrument while decreasing exposure of the operator to irritating fumes.

Formaldehyde is available as a 40% weight per volume solution in water (100% **formalin**). An 8% formaldehyde solution in water has a broad spectrum of activity against bacteria, fungi, and viruses. Sporicidal activity may take as long as 18 hours. Its rapidity of action is increased by solution in 70% isopropanol. Formaldehyde solutions are used for high-level disinfection of hemodialyzers, preparation of vaccines, and preservation and embalming of tissues. The 4% formaldehyde (10% formalin) solutions used for fixation of tissues and embalming may not be mycobactericidal.

Glutaraldehyde is a dialdehyde (1,5-pentanedial). Solutions of 2% weight per volume glutaraldehyde are most commonly used. The solution must be alkalinized to pH 7.4–8.5 for activation. Activated solutions are bactericidal, sporicidal, fungicidal, and virucidal for both lipophilic and hydrophilic viruses. Glutaraldehyde has greater sporicidal activity than formaldehyde, but its tuberculocidal activity may be less. Lethal action against mycobacteria and spores may require prolonged exposure. Once activated, solutions have a shelf life of 14 days, after which polymerization reduces activity. Other means of activation and stabilization can increase the shelf life. Because glutaraldehyde solutions are frequently reused, the most common reason for loss of activity is dilution and exposure to organic material. Test strips to measure residual activity are recommended.

Formaldehyde has a characteristic pungent odor and is highly irritating to respiratory mucous membranes and eyes at concentrations of 2–5 ppm. The United States Occupational Safety and Health Administration (OSHA) has declared that formaldehyde is a potential carcinogen and has established an employee exposure standard that limits the 8-hour time-weighted average (TWA) exposure to 0.75 ppm. Protection of health care workers from exposure to glutaraldehyde concentrations greater than 0.2 ppm is advisable. Increased air exchange, enclosure in hoods with exhausts, tight-fitting lids on exposure devices, and use of protective personal equipment such as goggles, respirators, and gloves may be necessary to achieve these exposure limits.

Ortho-phthalaldehyde (OPA) is a phenolic dialdehyde chemical sterilant with a spectrum of activity comparable to glutaraldehyde, although it is several times more rapidly bactericidal. OPA solution typically contains 0.55% OPA. Its label claim is that high-level disinfection can be achieved in 12 minutes at room temperature compared with 45 minutes for 2.4% glutaraldehyde. Unlike glutaraldehyde, OPA requires no activation, is less irritating to mucous membranes, and does not require exposure monitoring. It has good materials compatibility and an acceptable environmental safety profile. OPA is useful for disinfection or sterilization of endoscopes, surgical instruments, and other medical devices.

SUPEROXIDIZED WATER

Electrolysis of saline yields a mixture of oxidants, primarily hypochlorous acid and chlorine, with potent disinfectant and sterilant properties. The solution generated by the process, which has been commercialized and marketed as Sterilox for disinfection of endoscopes and dental materials, is rapidly bactericidal, fungicidal, tuberculocidal, and sporicidal. High-level disinfection is achieved with a contact time of 10 minutes. The solution is nontoxic and nonirritating and requires no special disposal precautions.

PEROXYGEN COMPOUNDS

The peroxygen compounds, **hydrogen peroxide** and **peracetic acid,** have high killing activity and a broad spectrum against bacteria, spores, viruses, and fungi when used in appropriate concentration. They have the advantage that their decomposition products are not toxic and do not injure the environment. They

are powerful oxidizers that are used primarily as disinfectants and sterilants.

Hydrogen peroxide is a very effective disinfectant when used for inanimate objects or materials with low organic content such as water. Organisms with the enzymes catalase and peroxidase rapidly degrade hydrogen peroxide. The innocuous degradation products are oxygen and water. Concentrated solutions containing 90% weight per volume H_2O_2 are prepared electrochemically. When diluted in high-quality deionized water to 6% and 3% and put into clean containers, they remain stable. Hydrogen peroxide has been proposed for disinfection of respirators, acrylic resin implants, plastic eating utensils, soft contact lenses, and cartons intended to contain milk or juice products. Concentrations of 10–25% hydrogen peroxide are sporicidal. Vapor phase hydrogen peroxide (VPHP) is a cold gaseous sterilant that has the potential to replace the toxic or carcinogenic gases ethylene oxide and formaldehyde. VPHP does not require a pressurized chamber and is active at temperatures as low as 4°C and concentrations as low as 4 mg/L. It is incompatible with liquids and cellulose products. It penetrates the surface of some plastics. Automated equipment using vaporized hydrogen peroxide (eg, Sterrad) or hydrogen peroxide mixed with formic acid (Endoclens) is available for sterilizing endoscopes.

Peracetic acid (CH_3COOOH) is prepared commercially from 90% hydrogen peroxide, acetic acid, and sulfuric acid as a catalyst. It is explosive in the pure form. It is usually used in dilute solution and transported in containers with vented caps to prevent increased pressure as oxygen is released. Peracetic acid is more active than hydrogen peroxide as a bactericidal and sporicidal agent. Concentrations of 250–500 ppm are effective against a broad range of bacteria in 5 minutes at pH 7.0 at 20°C. Bacterial spores are inactivated by 500–30,000 ppm peracetic acid. Only slightly increased concentrations are necessary in the presence of organic matter. Viruses require variable exposures. Enteroviruses require 2000 ppm for 15–30 minutes for inactivation.

An automated machine (Steris) that uses buffered peracetic acid liquid of 0.1–0.5% concentration has been developed for sterilization of medical, surgical, and dental instruments. Peracetic acid sterilization systems have also been adopted for hemodialyzers. The food processing and beverage industries use peracetic acid extensively because the breakdown products in high dilution do not produce objectionable odor, taste, or toxicity. Because rinsing is not necessary in this use, time and money are saved.

Peracetic acid is a potent tumor promoter but a weak carcinogen. It is not mutagenic in the Ames test.

HEAVY METALS

Heavy metals, principally mercury and silver, are now rarely used as disinfectants. Mercury is an environmental hazard, and some pathogenic bacteria have developed plasmid-mediated resistance to mercurials. Hypersensitivity to thimerosal is common, possibly in up to 40% of the population. These compounds are absorbed from solution by rubber and plastic closures. Nevertheless, **thimerosal** 0.001–0.004% is still used safely as a preservative of vaccines, antitoxins, and immune sera. Although a causative link to autism has never been established, thimerosal-free vaccines are available for use in children and pregnant woman.

Inorganic silver salts are strongly bactericidal. **Silver nitrate,** 1:1000, has been most commonly used, particularly as a preventive for gonococcal ophthalmitis in newborns. Antibiotic ointments have replaced silver nitrate for this indication. **Silver sulfadiazine** slowly releases silver and is used to suppress bacterial growth in burn wounds (see Chapter 46).

STERILANTS

For many years, pressurized **steam (autoclaving)** at 120°C for 30 minutes has been the basic method for sterilizing instruments and other heat-resistant materials. When autoclaving is not possible, as with lensed instruments and materials containing plastic and rubber, **ethylene oxide**—diluted with either fluorocarbon or carbon dioxide to diminish explosive hazard—is used at 440–1200 mg/L at 45–60°C with 30–60% relative humidity. The higher concentrations have been used to increase penetration.

Ethylene oxide is classified as a mutagen and carcinogen. The OSHA permissible exposure limit (PEL) for ethylene oxide is 1 ppm calculated as a time-weighted average. Alternative sterilants now being used increasingly include vapor phase hydrogen peroxide, peracetic acid, ozone, gas plasma, chlorine dioxide, formaldehyde, and propylene oxide. Each of these sterilants has potential advantages and problems. Automated peracetic acid systems are being used increasingly for high-level decontamination and sterilization of endoscopes and hemodialyzers because of their effectiveness, automated features, and the low toxicity of the residual products of sterilization.

PRESERVATIVES

Disinfectants are used as preservatives to prevent the overgrowth of bacteria and fungi in pharmaceutical products, laboratory sera and reagents, cosmetic products, and contact lenses. Multi-use vials of medication that may be reentered through a rubber diaphragm, and eye and nose drops, require preservatives. Preservatives should not be irritating or toxic to tissues to which they will be applied, they must be effective in preventing growth of microorganisms likely to contaminate them, and they must have sufficient solubility and stability to remain active.

Commonly used preservative agents include organic acids such as **benzoic acid** and salts, the **parabens,** (alkyl esters of *p*-hydroxybenzoic acid), sorbic acid and salts, phenolic compounds, quaternary ammonium compounds, alcohols, and mercurials such as thimerosal in 0.001–0.004% concentration.

SUMMARY Miscellaneous Antimicrobials

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
NITROIMIDAZOLE				
• Metronidazole	Disruption of electron transport chain	Bactericidal activity against susceptible anaerobic bacteria and protozoa	Anaerobic infections • vaginitis • *C difficile* colitis	Oral or IV • hepatic clearance (half-life = 8 h) • disulfiram-like reaction when given with alcohol • *Toxicity:* Gastrointestinal upset • metallic taste • neuropathy • seizures
• *Tinidazole: Oral; similar to metronidazole but dosed once daily; approved for trichomonas, giardiasis, and amebiasis*				
URINARY ANTISEPTICS				
• Nitrofurantoin	Not fully understood • disrupts protein synthesis and inhibits multiple bacterial enzyme systems	Bacteriostatic or bactericidal activity against susceptible bacteria	Uncomplicated urinary tract infections • long-term prophylaxis	Oral • rapid renal clearance (half-life = 0.5 h) • blood levels are negligible • contraindicated in renal failure • *Toxicity:* Gastrointestinal upset • neuropathies • hypersensitivity in patients with pulmonary fibrosis
• *Methenamine hippurate and methenamine mandelate: Oral; release formaldehyde at acidic pH in the urine; used only for suppression, not treatment, of urinary tract infections*				
MACROLIDE				
• Fidaxomicin	Inhibits bacterial RNA polymerase	Bactericidal in gram positive bacteria	*C difficile* colitis	Oral • blood levels negligible

PREPARATIONS AVAILABLE

MISCELLANEOUS ANTIMICROBIAL DRUGS

Colistimethate sodium (Coly-Mycin M)
Parenteral: 150 mg for injection

Fidaxomicin (Dificid)
Oral: 200 mg tablets

Methenamine hippurate (Hiprex, Urex)
Oral: 1.0 g tablets

Methenamine mandelate (generic)
Oral: 0.5, 1 g tablets; 0.5 g/5 mL suspension

Metronidazole (generic, Flagyl)
Oral: 250, 500 mg tablets; 375 mg capsules; 750 mg extended-release tablets
Topical: 0.75% gel
Parenteral: 5 mg/mL; 500 mg for injection

Mupirocin (Bactroban)
Topical: 2% ointment, cream

Nitrofurantoin (generic, Macrodantin)
Oral: 25, 50, 100 mg capsules, 25 mg/5 mL suspension

Polymyxin B (Polymyxin B Sulfate)
Parenteral: 500,000 units per vial for injection
Ophthalmic: 500,000 units per vial

DISINFECTANTS, ANTISEPTICS, & STERILANTS

Benzalkonium (generic, Zephiran)
Topical: 17% concentrate; 50% solution; 1:750 solution

Benzoyl peroxide (generic)
Topical: 2.5%, 5%, 10% liquid; 5%, 5.5%, 10% lotion; 5%, 10% cream; 2.5%, 4%, 5%, 6%, 10%, 20% gel

Chlorhexidine gluconate (Hibiclens, Hibistat, others)
Topical: 2%, 4% cleanser, sponge; 0.5% rinse in 70% alcohol
Oral rinse (Peridex, Periogard): 0.12%

Glutaraldehyde (Cidex)
Instruments: 2%, 3.2% solution

Hexachlorophene (pHisoHex)
Topical: 3% liquid; 0.23% foam

Iodine aqueous (generic, Lugol's Solution)
Topical: 2–5% in water with 2.4% sodium iodide or 10% potassium iodide

Iodine tincture (generic)
Topical: 2% iodine or 2.4% sodium iodide in 47% alcohol, in 15, 30, 120 mL and in larger quantities

Nitrofurazone (generic, Furacin)
Topical: 0.2% solution, ointment, and cream

Ortho-phthalaldehyde (Cidex OPA)
Instruments: 0.55% solution

Povidone-iodine (generic, Betadine)
Topical: available in many forms, including aerosol, ointment, antiseptic gauze pads, skin cleanser (liquid or foam), solution, and swabsticks

Silver nitrate (generic)
Topical: 10, 25, 50% solution

Thimerosal (generic, Mersol)
Topical: 1:1000 tincture and solution

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CASE STUDY ANSWER

The patient should be treated with oral metronidazole, which is considered the preferred drug for mild to moderate cases of *C difficile*-associated colitis. The room should not be cleaned with alcohol since it does not kill *C difficile* spores. A concentrated bleach solution (5000 ppm) would be preferred because it is sporicidal.