TABLE 39.4 Mechanism of Action and Recognized Mutational Resistance in Commonly Used Antituberculous Agents

DRUG	MECHANISM OF ACTION	SITE OF MUTATIONAL RESISTANCE (GENE)
Isoniazid	Inhibits mycolic acid synthesis	*inhA* (regulatory region) (mycolic acid gene)
	Catalase/peroxidase enzyme	*katG* (catalase/peroxidase gene)
Rifampin	Inhibits RNA polymerization	β-subunit *rpoB* (RNA polymerase gene)
Pyrazinamide	Unknown	*pncA* (pyrazinamidase gene)
Ethambutol	Inhibits cell wall synthesis (blocks arabinosyl transferase)	*embB* (gene for arabinosyl transferase enzyme)
Streptomycin	Inhibits protein synthesis	*rpsL* (gene for ribosomal S12 protein); 16S ribosomal RNA gene
Amikacin	Inhibits protein synthesis	16S ribosomal RNA gene (*Mycobacterium tuberculosis* and *Mycobacterium avium* complex)
Capreomycin	Inhibits cell wall synthesis	Unknown
Quinolones	Inhibit DNA structure	*gyrA* (gyrase A gene)
Macrolides	Inhibit protein synthesis	23S rRNA gene (*M. avium* complex, *Mycobacterium abscessus* subsp.)

pyrazinamidase *(pncA)* (Table 39.4).[69,70] This results in the loss of pyrazinamidase activity, an enzyme that converts PZA to the active form of pyrazinoic acid.

Pharmacology

PZA is well absorbed orally and widely distributed throughout the body, attaining concentrations above that needed to inhibit tubercle bacilli. Peak plasma concentrations are approximately 50 µg/mL, with a half-life of 12 hours, making once-daily or less frequent dosing practical. PZA crosses inflamed meninges and has been recommended in combination regimens for tuberculous meningitis.[71] It is metabolized by the liver, and metabolic products including principally pyrazinoic acid are excreted mainly by the kidneys, requiring dosage modification in renal failure. PZA is dialyzable, so dosing is recommended after dialysis sessions consistent with dosing recommendations for INH, rifampin, and ethambutol.[57]

Adverse Reactions

The most common side effects are nausea and vomiting. Hepatotoxicity occurred in nearly 15% of PZA recipients in early trials that employed dosages of 40 to 50 mg/kg/day for prolonged periods. Current regimens of 20 to 35 mg/kg/day are safer,[72] although more recent data suggest that PZA is the most common cause of hepatotoxicity in multidrug regimens also containing INH and rifampin.[73,74] Patients with preexisting liver disease should have symptoms and hepatic function tests monitored closely. PZA is also a frequent cause of hypersensitivity reactions and nongouty polyarthralgia in these multidrug regimens.[73] Other adverse reactions (1% of patients or less) include interstitial nephritis,[75] rhabdomyolysis with myoglobinuric renal failure,[76] and photosensitivity. Asymptomatic urate retention occurs in 50% of PZA recipients, with symptomatic gout usually occurring in patients with preexisting gout.[72]

Significant Drug Interactions

As just noted, the combination of rifampin and PZA for treatment of LTBI is associated with a high rate of severe or fatal hepatotoxicity.[63,64,65] There are no other significant drug interactions with PZA.

Usage

PZA is included as an essential component of multidrug 6-month short-course chemotherapy.[19,73] Without PZA for the first 2-month initiation phase of therapy, relapse rates after 6 months of therapy are unacceptable.[19] Efficacy with intermittent administration makes PZA suitable for directly observed therapy regimens. PZA is a class C drug and should be used with caution in pregnancy. Although PZA is recommended for routine use in pregnant women by the World Health Organization (WHO), the drug has not been recommended for general use in pregnant women in the United States by the FDA and the CDC because of insufficient data to determine safety.[19] The practical consequence of this policy is that pregnant women in the United States with active tuberculosis require 9 months of therapy because PZA is not included in the first 2 months of therapy. Most experts do not hesitate to include PZA in treatment regimens for pregnant patients with drug-resistant tuberculosis.

Availability and Dosage

PZA is available in 500-mg tablets or as 300-mg tablets in combination with INH (50 mg) and rifampin (120 mg) (Rifater). Dosage is 20 to 25 mg/kg/day (maximum 2.0 g) orally once or in two divided doses. PZA has been well tolerated in a twice-weekly dosage of 50 mg/kg (not to exceed 4 g/day) for short-course regimens.

Ethambutol

Derivation and Structure

Ethambutol (ethylenediiminobutanol) was discovered in 1961 among synthetic compounds screened for antituberculous activity.

Mechanism of Action

Ethambutol inhibits arabinosyl transferase enzymes that are involved in arabinogalactan and lipoarabinomannan biosynthesis within the cell wall.[77]

Antimicrobial Activity and Resistance

Ethambutol is bacteriostatic in vitro or within macrophages[67] at concentrations of 1 µg/mL against susceptible strains of *M. tuberculosis*. Primary ethambutol resistance in the United States is extremely unusual.[11,12] The principal role of ethambutol has been as a "companion" drug to curtail resistance. Specifically, ethambutol is included in the usual initial tuberculosis treatment regimen with INH, rifampin, and PZA for the possibility of unrecognized INH resistance. PZA alone is not an effective drug for preventing the emergence of rifampin resistance in the presence of INH resistance. Ethambutol is discontinued when INH and rifampin susceptibility are confirmed. Ethambutol resistance rates of 80% have been demonstrated with isolates with resistance to INH and rifampin, indicating a likely limited utility against MDR-TB.[2] Ethambutol resistance relates to point mutations in the arabinosyl transferase enzyme EmbB, which is coded for by the *embB* gene.[78]

Pharmacology

Ethambutol administered orally is 75% to 80% absorbed, yielding peak plasma concentrations of 5 µg/mL after a dose of 25 mg/kg. It is distributed throughout the body including the CSF. Although little ethambutol crosses normal meninges, levels 10% to 50% of those in plasma occur in CSF with meningeal inflammation. After conversion of approximately 25% of absorbed ethambutol to inactive metabolites, 80% of the parent drug, together with metabolites, is excreted in urine. Consequently, it becomes necessary to modify the dosage in significant renal failure.

Adverse Reactions

The major toxicity of ethambutol is neuropathy, including peripheral neuropathy and retrobulbar optic neuritis. Characteristically, patients complain of bilateral blurry vision and are found to have impairment of visual acuity and red-green color vision. Common in association with high-dose (50 mg/kg/day) therapy with prolonged administration and more common with 25 mg/kg/day than with 15 mg/kg/day dosing, retrobulbar neuritis is usually slowly reversible. Visual loss has rarely occurred in elderly patients receiving 15 mg/kg/day.[79] The administration of ethambutol at 25 mg/kg on a three-times-weekly basis appears to be associated with a reduced risk for visual toxicity in this patient population

compared with daily dosing at 15 mg/kg.[80] This observation is important because baseline visual acuity is often impaired in older patients and is associated with other ocular problems, such as cataracts, also associated with blurred vision. Recipients of ethambutol should be instructed to report symptoms of blurry vision or color vision abnormalities promptly and to discontinue the drug until confirmatory visual testing can be done. Visual acuity and red-green color perception testing is recommended at baseline, whenever a change in visual symptoms occurs, and monthly for patients taking ethambutol for more than 2 months or at higher than usual doses.[19] Monthly testing in patients receiving 15 mg/kg can be useful in establishing the range of visual abnormalities in those already visually impaired.

Gastrointestinal intolerance is infrequent. Hyperuricemia occurs because of decreased renal uric acid excretion. Hypersensitivity reactions are rare and include dermatitis, arthralgias, and fever.

Significant Drug Interactions

There are no significant drug interactions with ethambutol.

Usage

Ethambutol is routinely included as the fourth drug along with INH, rifampin, and PZA in initial therapy for tuberculosis before the availability of drug susceptibility information. As described in "Antimicrobial Activity and Resistance," ethambutol is included to protect against the emergence of rifampin resistance in patients with occult INH resistance who, if receiving only INH, rifampin, and PZA, would be functionally on only INH and PZA. It is also routinely used in treatment regimens for patients with isolates resistant to INH or rifampin or both. Ethambutol has no detectable effects on the fetus and is approved for treatment of tuberculosis in the United States.

Availability and Dosage

Ethambutol is available as ethambutol hydrochloride (Myambutol) supplied in 100-mg or 400-mg tablets. The usual dosage is 15 mg/kg/day as a single daily dose or 25 mg/kg three times weekly.

Streptomycin

Derivation, Structure, and Pharmacology

Streptomycin, an aminoglycoside antibiotic introduced in the 1940s, was the first drug to reduce tuberculosis mortality. Its structure, mechanism of action, and pharmacology are discussed in other chapters. Briefly, intramuscular injection of 1 g yields peak plasma concentrations of 25 to 45 µg/mL. It is virtually excluded from the CNS.

Antimicrobial Activity and Resistance

Streptomycin is bactericidal against *M. tuberculosis* in vitro but is inactive against intracellular tubercle bacilli. Concentrations of 4 to 10 µg/mL of plasma are inhibitory. The rapid emergence of resistance to streptomycin was quickly recognized as a consequence of single-drug therapy. Approximately 1 in 10^6 tubercle bacilli is spontaneously resistant to streptomycin. Primary resistance to streptomycin is seen most often in patient populations having a high incidence of INH resistance. In MDR-TB disease outbreaks, approximately 80% of isolates resistant to INH and rifampin are also resistant to streptomycin.[2] Streptomycin resistance relates to mutational changes involving ribosomal binding protein or the ribosomal binding site.[27,81,82] Isolates resistant to streptomycin are not cross-resistant to amikacin, kanamycin, or capreomycin.

Adverse Reactions

Streptomycin toxicity is similar to that of other aminoglycoside antibiotics but with less renal and auditory toxicity and greater vestibular toxicity than more commonly used aminoglycosides. Patients receiving streptomycin should be instructed to be aware of tinnitus, decreased hearing, and problems with balance, and they should be instructed to notify their caregiver immediately if such reactions occur.

In contrast to other aminoglycosides, allergic or hypersensitivity reactions can be seen with streptomycin. These include fever, chills, eosinophilia, and rash.

Significant Drug Interactions

There are no significant drug interactions with streptomycin.

Usage

Streptomycin is most commonly indicated as part of multidrug therapy for drug-resistant tuberculosis. A high prevalence of streptomycin resistance in patients who have received it as part of antituberculosis therapy outside the United States has limited its utility for treating drug-resistant tuberculosis in the United States. Additionally, the lack of availability of streptomycin levels for guiding streptomycin dosing versus the widespread availability of amikacin levels has further diminished its use in the United States. Dosages greater than 1 g/day should be avoided. Reduction in dosage or frequency of administration or both is indicated in patients older than 50 years, patients with low body weight, and patients in whom renal function is impaired. Streptomycin blood levels may be useful for guiding streptomycin dosing in these circumstances. Special care must be taken when streptomycin is used in combination with other nephrotoxic or ototoxic drugs, such as capreomycin or amikacin. It is a category D drug in pregnancy because of fetal ototoxicity.

Primary resistance to streptomycin is significant in isolates from individuals from some countries. Cross-resistance is not seen between streptomycin and amikacin, so unless patients have had prior treatment with either kanamycin or amikacin, streptomycin-resistant isolates should remain susceptible to amikacin.[66a]

Availability and Dosage

Streptomycin sulfate for intramuscular injection is provided in 1-g single-injection vials. The recommended dosage in younger adults (<50 years old) with normal renal function is 15 mg/kg/day or 0.5 to 1 g daily to 1 g twice weekly. Children receive 20 to 40 mg/kg/day (maximum 1 g) in divided doses every 12 hours. Although not approved for such use, the drug can be safely given intravenously when needed.

ALTERNATIVES TO RIFAMPIN

Rifabutin

Derivation and Pharmacology

Several spiropiperidyl rifamycins have activity against mycobacteria, including *M. tuberculosis, Mycobacterium avium-intracellulare* complex (MAC), and *Mycobacterium kansasii*.[83,84,85,86,87] Rifabutin (Mycobutin), a derivative of rifamycin-S, is more active in vitro and more effective on a weight basis in experimental murine tuberculosis than rifampin.[86] The mechanism of action is inhibition of RNA polymerase, as it is with rifampin. It has a long plasma half-life (45 hours) in humans and marked tissue tropism, producing tissue concentrations 5-fold to 10-fold greater than in serum. Peak serum concentrations of rifampin (5–10 µg/mL) are 5-fold to 10-fold higher than those of rifabutin (0.5 µg/mL).[88]

Adverse Reactions

Polymyalgia syndrome, yellowish tan discoloration of the skin (pseudojaundice), and anterior uveitis have occurred in patients taking rifabutin, usually at doses exceeding 300 mg daily.[89,90] Almost all patients with these side effects have also been receiving clarithromycin, fluconazole, or ritonavir. Symptoms of uveitis include ocular pain and blurred vision.[90] Neutropenia and thrombocytopenia are dose dependent and occur in up to one-third of patients receiving therapy for pulmonary MAC disease.[91] The incidence of rash, hepatitis, and gastrointestinal distress appears comparable to that with rifampin. Rifabutin also can produce an orange-red discoloration of urine, saliva, tears, and contact lenses similar to rifampin.

Significant Drug Interactions

Rifabutin induces the hepatic cytochrome P-450 system, but only about 50% of that seen with rifampin. This induction produces lowered serum levels of numerous drugs normally metabolized in the liver, including PIs (Table 39.5).[13,17] Concurrent administration of delavirdine or saquinavir with rifabutin is not recommended for this reason.[92] Rifabutin is also metabolized by this same system, so enzyme inhibitors such as the PIs fluconazole and clarithromycin increase plasma rifabutin concentrations (see Table 39.3).[13,17,89,92]

TABLE 39.5 Recommendations for Coadministering Antiretroviral Drugs With Rifabutin

	ANTIRETROVIRAL DOSE CHANGE	RIFABUTIN DOSE CHANGE	COMMENTS
Non-Nucleoside Reverse-Transcriptase Inhibitors			
Efavirenz	No change	Change to 450–600 mg (daily or intermittent)	Rifabutin AUC ↓ by 38%. Effect of efavirenz + PI on rifabutin concentration has not been studied. Efavirenz should not be used during first trimester of pregnancy
Nevirapine	No change	No change (300 mg daily or 3 times/wk)	Rifabutin and nevirapine AUC not significantly changed
Rilpivirine	Rifabutin and rilpivirine should not be used together		Rilpivirine AUC ↓ by 46%
Etravirine	No change	No change (300 mg daily or 3 times/wk)	No clinical experience; etravirine C_{min} ↓ by 45%, but this was not thought to warrant a change in dose
Single PIs			
Fosamprenavir	No change	↓ to 150 mg/day or 300 mg 3 times/wk	No published clinical experience
Atazanavir	No change	↓ to 150 mg every other day or 3 times/wk	No published clinical experience. Rifabutin AUC ↑ by 250%
Indinavir	1000 mg q8h	↓ to 150 mg/day or 300 mg 3 times/wk	Rifabutin AUC ↑ by 170%; indinavir concentrations ↓ by 34%
Nelfinavir	No change	↓ to 150 mg/day or 300 mg 3 times/wk	Rifabutin AUC ↑ by 207%; insignificant change in nelfinavir concentration
Dual PI Combinations			
Lopinavir/ritonavir (Kaletra)	No change	↓ to 150 mg every other day or 3 times/wk	Rifabutin AUC ↑ by 303%; 25-*O*-desacetyl rifabutin AUC ↑ by 47.5-fold
Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fosamprenavir, atazanavir, tipranavir, or darunavir	No change	↓ to 150 mg every other day or 3 times/wk	Rifabutin AUC and 25-*O*-desacetyl rifabutin AUC ↑, by varying degrees
CCR-5 Receptor Antagonists			
Maraviroc	No change	No change	No clinical experience; significant interaction is unlikely
Integrase Inhibitors			
Raltegravir	No change	No change	No clinical experience; significant interaction is unlikely
Dolutegravir	No change	No change	No clinical experience; significant interaction is unlikely
Elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild)	Coadministration should be avoided		Consider alternative antimycobacterial or alternative antiviral regimen. If used, consider rifabutin 150 mg once daily or every other day. Monitor rifabutin concentrations, and adjust dose accordingly. Elvitegravir AUC ↓ 21%, C_{min} ↓ 67%; rifabutin active metabolite (25-*O*-desacetyl rifabutin) AUC ↑ 625%

[a]For the most up-to-date information, see https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/325/tb.
AUC, Area under the curve; *C_{min},* trough concentration; *PI,* protease inhibitor.

Usage

Rifabutin appears as effective as rifampin in the treatment of drug-susceptible tuberculosis.[93,94] In patients with HIV infection, rifampin is replaced by rifabutin if PIs are used (amprenavir, atazanavir, darunavir, fosamprenavir, nelfinavir, lopinavir-ritonavir [Kaletra], tipranavir-ritonavir, darunavir-ritonavir, and ritonavir).[13,17] Current guidelines suggest that rifabutin should be given as 300 mg three times a week or every other day with the option for monitoring rifabutin levels.[13] Rifabutin's potential for treatment of infection with MDR-TB is of interest because approximately 25% of rifampin-resistant tuberculosis strains are inhibited by low concentrations of rifabutin. Molecular methods for rifampin susceptibility testing have identified strains of *M. tuberculosis* with selected mutations that are rifampin resistant but with MIC values only slightly above the usual MIC. These strains may test as susceptible to rifampin on liquid media but usually are reported as resistant if tested on solid media. These isolates usually are reported as susceptible to rifabutin at 2.0 μg/mL. Some data suggest that rifabutin adds to the efficacy of treatment regimens in this circumstance, although other studies have reported poor outcomes including treatment failure, relapse, and further acquisition of drug resistance associated with the presence of these mutations.[95,96] It remains controversial whether patients with rifampin-resistant/rifabutin-susceptible *M. tuberculosis* can be treated for shorter durations than other patients with rifampin-resistant *M. tuberculosis*, especially patients with concomitant INH resistance. Until there is more supportive evidence, it seems prudent to include rifabutin in the regimens of these patients but not to assume that rifabutin has activity in this situation comparable to its activity for *M. tuberculosis* isolates without *rpoB* mutations.[97]

Rifapentine

Derivation and Pharmacology

With the microbiologic success of rifabutin but problems with low serum levels and complex adverse reactions, investigators searched for other rifamycin compounds. The most promising agent is rifapentine.[98–100] In the study leading to licensure in 1998, rifapentine, 600 mg twice weekly, was compared with rifampin, 450 to 600 mg, when both were given with daily INH, pyrazinamide, and ethambutol for 2 months followed by rifapentine, 600 mg, plus INH once weekly or rifampin, 450 to 600 mg, plus INH twice weekly. Results after 6 months were comparable, although the rifapentine relapse rate was slightly higher (10% vs. 5%).[99] When given with a fatty meal, peak blood levels after the administration of 600 mg of rifapentine are 15 μg/mL of native drug and 6 μg/mL of 25-desacetyl rifapentine, the active metabolite. The half-life of rifapentine is 13 hours.

Adverse Drug Reactions
The adverse effects of rifapentine are similar to those associated with rifampin.

Significant Drug Interactions
Rifapentine appears to be a more potent inducer of the cytochrome P-450 system than rifabutin but less than rifampin. Therefore it may increase metabolism of coadministered drugs that are metabolized by these enzymes.

Usage
Rifapentine has been approved for once-weekly use with INH in the continuation phase of therapy for HIV-negative patients without cavitation on chest radiograph and negative acid-fast bacilli smears at 2 months.[19] With recent interest in possible benefits of increased rifamycin exposure, tuberculosis therapy studies are ongoing with daily and higher dose rifapentine-containing regimens. In one study, daily rifapentine was found to be well tolerated and safe. The high rifapentine exposure was associated with enhanced sputum sterilization levels at completion of the intensive phase.[101] Rifapentine is contraindicated in HIV-seropositive patients on ART because of interaction with PIs and NNRTIs and the development of rifamycin monoresistance in some patients.[13,102] Rifapentine in combination with INH given once weekly for 12 weeks (12 total doses) has been shown to be as effective and safe as INH with higher treatment completion rates than INH for treating LTBI in HIV-seronegative and HIV-seropositive patients not on ART.[103,104] This combination in once-weekly therapy has more recently been shown effective in children 2 to 17 years of age.[105] Rifapentine use in LTBI therapy should be administered by directly observed therapy.

Availability and Dosage
Rifapentine is available in 150-mg tablets. The recommended dosage for adults in the continuation phase of therapy for tuberculosis has been 10 mg/kg or a maximum 600 mg per week, although studies are ongoing to determine the optimal dose for rifapentine with active tuberculosis disease. The recommended dose for LTBI therapy is 900 mg per week, but weekly doses of 1200 mg appear to be tolerated well. The drug is not approved for use in children or pregnant women. The pharmacokinetics of rifapentine have not been evaluated in patients with renal impairment. Only about 17% of an administered dose is excreted via the kidneys. The clinical significance of impaired renal function in the disposition of rifapentine is unknown. Similarly, the clinical significance of impaired hepatic function in the disposition of rifapentine and its 25-desacetyl metabolite is not known.

SECOND-LINE ANTITUBERCULOUS DRUGS

Quinolones (see Chapter 35)

Mechanism of Action
Emerging outbreaks of MDR-TB disease[2,3,4,5,6] stimulated the investigation of fluorinated quinolones for their activity against mycobacteria.[106–109] These drugs are bactericidal against both extracellular rapidly multiplying bacteria and intracellular nonmultiplying bacteria with achievable serum levels.[108] They inhibit bacterial DNA gyrase, an enzyme that is essential for the maintenance of DNA supercoils needed for chromosomal replication.[108] The fluoroquinolones penetrate well into alveolar macrophages, respiratory secretions, and body fluids with concentrations equal to or higher than those in serum. CNS penetration is good, allowing these drugs to be used for tuberculous meningitis.[10,14,110] The prolonged half-life (5–8 h for levofloxacin and 9–15 h for moxifloxacin) and significant postantibiotic effect allow once-daily dosing.[108]

Antimicrobial Activity and Resistance
Older quinolones ciprofloxacin and ofloxacin have both been associated with good outcomes in the treatment of drug-susceptible and drug-resistant tuberculosis.[10,14,111,112] Ciprofloxacin and ofloxacin inhibit more than 90% of strains of drug-susceptible tubercle bacilli at concentrations of 0.5 μg/mL and 1.0 μg/mL, respectively.[108,109] Clinical trials of ofloxacin in combination with INH and rifampin indicate activity comparable to ethambutol.[112] Usage of fluoroquinolones as a single agent in animal models or in human trials with inactive drugs has led to the rapid emergence of resistance. Resistance appears to result from mutations in the genes responsible for DNA configuration (DNA gyrase).[27,113]

Ofloxacin and ciprofloxacin have relatively weak activity compared with the newer quinolones.[10,14] Of the quinolones, gatifloxacin (no longer marketed in the United States), moxifloxacin, and levofloxacin, in that order, have the most activity against *M. tuberculosis* with significant early bactericidal activity against *M. tuberculosis* relative to first-line antituberculous drugs.[108,114] Moxifloxacin and levofloxacin have lower MIC_{90} values (MIC required to inhibit the growth of 90% of organisms; 0.25 mg/L and 0.5–1 mg/L) than ciprofloxacin (4 mg/L) and ofloxacin (2 mg/L).[115,116] Furthermore, moxifloxacin has demonstrated early bactericidal activity in sputum that is equivalent to rifampin at 2 days and to INH at 5 days.[117] Despite the absence of prospective clinical trials using fluoroquinolones for MDR-TB, there has been considerable experience with levofloxacin and moxifloxacin, and they are regarded as critical to good treatment outcomes.[10,14,118]

The optimal quinolone and dose are still unclear, as higher doses of levofloxacin (750–1200 mg) are undergoing evaluation. The usual dose of moxifloxacin is 400 mg, which has good bactericidal activity.[115,116] Higher doses of 600 to 800 mg have been used to enhance CNS penetration during the treatment of MDR-TB meningitis and when the MIC of moxifloxacin is >0.5 μg/mL but <2.0 μg/mL.

Two phase II studies sponsored by the CDC have been conducted to evaluate the effect of moxifloxacin substitution for either ethambutol or INH during the first 2 months of treatment of newly diagnosed tuberculosis.[119,120] In the first trial, moxifloxacin substitution for ethambutol resulted in no apparent effect on 2-month sputum conversion rates to negativity but did show a faster median time to sputum conversion.[119] In a second trial, moxifloxacin substituted for INH in the first 2 months of treatment of tuberculosis had no effect on 2-month sputum conversion rates.[120] These studies suggest that substitution of moxifloxacin for ethambutol or INH during the first 2 months of therapy is no less efficacious than standard intensive-phase therapy and may result in more rapid clearance of *M. tuberculosis* from the lungs. A study comparing the replacement of INH with moxifloxacin (and rifampin with rifapentine) with both moxifloxacin and rifapentine given once weekly for the last 4 months of a 6-month course of therapy found this regimen to be noninferior to the current standard 6-month therapy.[121] However, two studies attempting to shorten the 6-month course of therapy for pulmonary tuberculosis to 4 months by replacing INH or ethambutol with moxifloxacin or gatifloxacin did not show noninferiority in any of the regimens compared with the 6-month standard therapy.[122,123]

Ofloxacin is the class drug used for determining quinolone susceptibility. Cross-resistance has been demonstrated among ciprofloxacin, ofloxacin, and levofloxacin. Resistance to quinolones develops rapidly when they are used as monotherapy.[124] Some quinolone-resistant isolates show susceptible MICs for moxifloxacin. The overall significance of this observation is not yet clear, but it suggests that moxifloxacin may still be an important element of therapy for some patients with XDR-TB.

Usage
Quinolones are now routinely incorporated into treatment regimens for MDR-TB disease along with other agents and are the cornerstones of therapy for quinolone-susceptible MDR-TB isolates. The usual dosage is levofloxacin, 750 to 1000 mg/day, or moxifloxacin, 400 mg/day. The use of quinolones in children and adolescents has not been approved, but most experts agree that the drugs should be considered for children with MDR-TB disease.[21] This class of drugs should be avoided in pregnancy. Fluoroquinolones are cleared primarily by the kidney, and dosage adjustment is recommended if creatinine clearance is less than 50 mL/min. They are not cleared by hemodialysis, so supplemental doses after dialysis are not necessary. Drug levels are not affected by hepatic disease. There is also ongoing concern about the use of quinolones as first-line therapy for community-acquired pneumonia, which is the most common misdiagnosis applied to missed cases of tuberculosis. It appears that either multiple or prolonged courses of quinolones are required to promote quinolone-resistant tuberculosis, which is not a circumstance without precedent.

Adverse Reactions

The adverse effects for quinolone include nausea and bloating, dizziness, insomnia, tremulousness, headache, rash, pruritus, and photosensitivity. Toxicity with the quinolone class of drugs most commonly is reported as gastrointestinal upset such as nausea and bloating. Myalgia is relatively common; rarely, tendon rupture has been reported.[10,14] An important consideration for long-term safety of the newer quinolones is their cardiac effect on the QT interval, resulting in a ventricular tachycardia known as torsades de pointes. The optimal approach for monitoring possible cardiac toxicity in patients on long-term quinolone therapy is not established. Whether to continue a quinolone in the presence of QT-interval prolongation or whether to add another agent that also may prolong the QT interval is clearly a risk-benefit decision, especially for patients with MDR-TB disease for which the quinolone may be the most important drug in the treatment regimen. Tendinitis and tendon rupture are also concerns with fluoroquinolones, which has prompted a special warning by the FDA on package inserts for fluoroquinolone use. As with potential cardiac toxicity, the decision to continue a quinolone in a patient with tendinitis requires an individualized risk-benefit analysis. Prolongation of the QT interval has been noted in patients taking moxifloxacin, but to our knowledge or in our experience it has not been reported in patients taking this drug for MDR-TB.

Significant Drug Reactions

Because antacids and other medications containing divalent cations markedly decrease absorption of fluoroquinolones, it is important that a fluoroquinolone not be administered within 2 hours of such medication.

Linezolid (see Chapter 33)

Linezolid is an oxazolidinone with activity against drug-resistant gram-positive bacteria. It has been shown to inhibit all strains of *M. tuberculosis* at concentrations of less than 1 μg/mL in vitro.[125] Although it has potentially severe toxicity with long-term use, it has been shown to have significant activity in multidrug regimens for MDR-TB and XDR-TB. Several studies have shown improved outcomes from linezolid in patients with tuberculosis with extensive resistance, even when added to a chronically failing regimen as salvage therapy.[126,127,128–130] The dosage of linezolid for bacterial infections is 600 mg twice daily, but most studies have used 600 mg once daily for treatment of tuberculosis in an effort to limit toxicity and cost. Serum drug levels are sufficiently above the MIC with this dosage.[126] In a series of 41 patients with XDR-TB unresponsive to therapy, linezolid at initial dosages of 600 mg/day followed by either 600 mg/day or 300 mg/day was associated with a sputum conversion rate of 87%.[127] Acquired linezolid resistance occurred in less than 10% of patients with both 300-mg and 600-mg linezolid dosing. Remarkably, 82% of patients had clinically significant adverse events but only 3 patients permanently discontinued linezolid because of drug toxicity.[127]

Most studies show that frequent significant adverse events occur in patients treated with 600 mg once daily of linezolid. These reactions, which are caused by inhibition of mitochondrial protein synthesis, include myelosuppression, peripheral and optic neuropathy, and lactic acidosis.[131,132,133] Most linezolid toxicity was reversible after stopping the drug but peripheral neuropathy has been especially concerning, as it may persist after stopping treatment.[131,132,133] Favorable outcomes and decreased toxicity compared with the 600 mg/day dosage have been reported for patients treated with a 300 mg/day dosage.[127]

Linezolid is associated with the serotonin syndrome in 25% of patients given selective serotonin reuptake inhibitors or other medications that increase serotonin concentrations in the CNS.[134] Patients should also be counseled to avoid foods, dietary supplements, and beverages high in tyramine.

Linezolid is marketed as Zyvox and is available as 600-mg tablets and infusions. The usual daily dosage for bacterial infections has been 600 mg twice daily. However, the usual dosage for tuberculosis is 300 to 600 mg once daily. The oral form is almost 100% bioavailable. The emergence of mutational resistance is not surprising because the drug inhibits the ribosome, and *M. tuberculosis* has only one copy of this gene.

Even in the context of its potential toxicity, linezolid is an important addition to the list of available medications for treating drug-resistant tuberculosis. It is superior to the relatively weak and toxic older second-line drugs such as cycloserine, ethionamide, and PAS and should be used instead of those medications in the absence of a specific contraindication.

Capreomycin, Amikacin, and Kanamycin

Capreomycin, amikacin, and kanamycin are considered as a group because all are administered by intramuscular or intravenous injection, have similar pharmacokinetics and toxicities, and are excreted by the renal route. These drugs have been used principally as alternative agents for MDR-TB disease. All have additive ototoxicity and nephrotoxicity and in that regard should be given cautiously similar to streptomycin or other aminoglycosides.

Capreomycin

Antimicrobial Activity and Resistance

Capreomycin, a polypeptide antibiotic obtained from *Streptomyces capreolus,* is active against *M. tuberculosis* including most MDR-TB strains[2] at concentrations of 1 to 50 μg/mL (usually 10 μg/mL). Average peak plasma concentrations of 30 μg/mL are achievable. There is no cross-resistance between streptomycin and capreomycin,[135] but some isolates resistant to kanamycin or amikacin are cross-resistant to capreomycin. The site of mutational change resulting in capreomycin resistance is unknown.

Adverse Reactions

Capreomycin can cause hearing loss, tinnitus, and decreased renal function but is considered less toxic than amikacin and especially kanamycin.

Significant Drug Interactions

There are no significant drug interactions with capreomycin.

Usage

Capreomycin has emerged as the first-line injectable agent in regimens for the treatment of drug-resistant tuberculosis, especially in the presence of streptomycin resistance.

Availability and Dosage

Capreomycin sulfate is supplied as Capastat. Dosing is the same as with streptomycin, with a range of 500 mg to 1 g deep intramuscularly five times weekly for 2 to 4 months in patients younger than 50 years and having normal renal function. Thereafter the dosage is reduced to 1 g two to three times weekly. It is a category C pregnancy drug.

Amikacin

Antimicrobial Activity and Resistance

In vitro and in animals, amikacin is among the most active aminoglycosides against *M. tuberculosis.* Because of its expense and greater toxicity, in the past it has been considered after streptomycin and capreomycin for the treatment of MDR-TB. However, several factors have made it the preferred parenteral agent including (1) the high rate of streptomycin resistance in MDR-TB isolates and (2) the ready availability of amikacin levels facilitating amikacin dosing that does not cause early severe toxicity and loss of the parenteral agent for long-term use. It has generally replaced kanamycin in the United States. Cross-resistance to amikacin and kanamycin results from an A-G change at base pair 1408 of the 16S ribosomal RNA gene.[136]

Recognition of this cross-resistance is important because, although kanamycin is rarely used in the United States, it is used more frequently outside the United States so that individuals from outside the country who received parenteral tuberculosis medications cannot be assumed to be susceptible to amikacin. However, kanamycin-resistant but amikacin-susceptible strains have been reported, emphasizing the importance of in vitro susceptibility testing regardless of prior antibiotic exposure.[137]

Adverse Reactions

Common side effects include tinnitus, hearing loss, and nonoliguric renal failure. Hypersensitivity events are rare.

Usage
Amikacin is an alternative injectable agent for the treatment of resistant *M. tuberculosis* infections. The customary dosage is 7 to 10 mg/kg (not to exceed 1 g) five times weekly. Because most pathology laboratories can determine blood levels of amikacin but not kanamycin, streptomycin, or capreomycin, amikacin is especially suited when parenteral therapy is required in patients with renal failure or in elderly patients with preexisting hearing loss. It is a category D drug in pregnancy.

Kanamycin
Kanamycin is an aminoglycoside that has activity against most strains of streptomycin-resistant tubercle bacilli. Except for its lower cost, kanamycin offers no advantage over amikacin in combination therapy and has substantial ototoxicity. In addition, serum levels are not readily available.

Availability and Dosage
Kanamycin sulfate is available as Kantrex, 0.5 g/2 mL, 1 g/3 mL, or 75 mg/2 mL (pediatric formulation) for intramuscular injection. The usual dose is 15 mg/kg (maximum 1.0 g), generally limited to 500 mg/day in adults because of ototoxicity.

Para-Aminosalicylic Acid
Derivation, Structure, and Pharmacology
As a calcium or sodium salt, this synthetic compound inhibits the growth of tubercle bacilli by the impairment of folate synthesis. PAS is incompletely absorbed orally. A 4-g dose yields plasma concentrations of 70 to 80 µg/mL. Of absorbed PAS, 85% is excreted in urine as various metabolic products.

Adverse Reactions
Chief among side effects of PAS is gastrointestinal intolerance, which is often severe and results in poor compliance. PAS can cause reversible drug-induced lupus-like reactivity and, when given as a sodium salt, sodium overload. It can produce lymphoid hyperplasia, and recipients can develop mononucleosis-like syndromes with fever, rash, hepatosplenomegaly, occasionally toxic hepatitis, and adenopathy. Hypersensitivity to PAS is frequent.

Usage
PAS has retained a limited role in multidrug therapy in developing countries because of its low cost. However, it is becoming less favored because of poor compliance and primary resistance. Its use in the United States is limited to the treatment of MDR-TB and XDR-TB disease.

Availability and Dosage
In the United States, PAS is available from the CDC (www.cdc.gov). Dosage forms include 500-mg tablets or 4-g resin packets. The usual dosage in adults is 10 to 12 g/day in three or four divided doses (6–8 g/day of the sodium potassium–free ascorbate) and in children 200 to 300 mg/kg/day in divided doses.

Cycloserine
Derivation and Mechanism of Action
By virtue of inhibiting cell wall synthesis, cycloserine possesses antimicrobial activity against a broad range of prokaryotic organisms including mycobacteria. In vitro, 5 to 20 g/mL inhibits susceptible *M. tuberculosis*.

Pharmacology
Cycloserine is readily absorbed orally. Serum concentration measurements aiming for a peak concentration of 20 to 35 mg/L are often useful in determining the optimal dose for a given patient. Widely distributed among tissues, no blood-brain barrier exists to cycloserine.[10,14,19] Little of the drug is metabolized, and approximately two-thirds is excreted unchanged by the kidneys.

Adverse Reactions
Cycloserine levels are essential for optimal use of this toxic drug. Peak serum concentrations of cycloserine should be kept between 20 and 35 µg/mL.[10,14,19] Cycloserine can cause peripheral neuropathy or CNS dysfunction including confusion, irritability, somnolence, headache, nervousness, vertigo, dysarthria, and seizures. Behavioral alterations include severe depression with suicidal ideation. Cycloserine is contraindicated in patients with a history of seizures or patients with severe underlying depression. Because the CNS toxicity appears to be dose related and only a few specialized laboratories do serum drug levels, the drug is generally avoided even by clinicians experienced in treating tuberculosis, unless no other options are available, such as with some patients infected with MDR-TB and XDR-TB strains.

Usage
Cycloserine is one of several alternatives for re-treatment regimens or for treatment of primary drug-resistant *M. tuberculosis*. It appears to have limited activity against MDR-TB strains.[2,10,14] It is classified as a category C drug in pregnancy.

Availability and Dosage
Cycloserine is provided in the United States as Seromycin in 250-mg pulvules. The usual dosage is 500 to 750 mg/day in two divided doses, with 500 mg/day commonly used. Cycloserine levels can be obtained to guide drug dosage and minimize toxicity.

Ethionamide
Derivation, Mechanism of Action, and Resistance
Ethionamide, a derivative of isonicotinic acid, was first synthesized in 1956. It is tuberculostatic at 0.6 to 2.5 µg/mL against susceptible strains, presumably by inhibition of oxygen-dependent mycolic acid synthesis.[138] The mechanism of ethionamide resistance is unknown, but some isolates are resistant to both INH and ethionamide and harbor mutations in the region of the *inhA* gene, which is involved in mycolic acid biosynthesis.[26]

Pharmacology
Ethionamide is absorbed well orally, yielding peak plasma concentrations of 20 µg/mL. It is widely distributed and penetrates both normal and inflamed meninges to yield CSF concentrations equivalent to those in plasma. It is metabolized by the liver, with metabolites renally excreted. Ethionamide interferes with INH acetylation.

Adverse Reactions
Gastrointestinal distress with nausea and vomiting frequently leads to poor compliance and drug discontinuance. Various neurologic disorders have been caused by ethionamide including peripheral neuropathy and psychiatric disturbances. Neurologic side effects have been reported to be alleviated by pyridoxine or nicotinamide. Reversible hepatotoxicity occurs in approximately 5% of ethionamide recipients. A hypersensitivity-type rash and poor diabetic control are infrequent complications. Its usage also is limited by a high frequency of severe gastrointestinal intolerance. Hypothyroidism is a recognized complication of ethionamide use and is more common when ethionamide is combined with PAS. Patients receiving long-term treatment with ethionamide should have periodic screening for hypothyroidism.

Usage
Ethionamide is among the agents that can be chosen for the treatment of drug-resistant tuberculosis. It appears to be active against most MDR-TB isolates. There is similarity in mode of action between ethionamide and INH, although their modes of action are sufficiently different that cross-resistance with clinical M. tuberculosis isolates usually does not occur. Regardless, confirmation of in vitro susceptibility to ethionamide for INH-resistant isolates must be obtained.

Availability and Dosage
Ethionamide is available in the United States as Trecator-SC in 250-mg coated tablets. The initial dosage is 250 mg twice daily (or as a single

dose at bedtime), which is increased by 250 mg daily until 1 g/day in divided doses is reached. Usually, 500 to 750 mg is the maximal tolerated dose.

β-Lactams

All mycobacteria produce β-lactamase. *M. tuberculosis* is protected from β-lactam antibiotics through its potent β-lactamase–encoded *gbya* gene called BlaC. Several β-lactamase–resistant β-lactam antibiotics are active in vitro against *M. tuberculosis*.[138–141] Clavulanate in particular has demonstrated in vitro the capacity to inhibit the activity of BlaC-encoded products. Meropenem, a carbapenem offering a limited substrate to hydrolysis, has demonstrated high bactericidal in vitro activity when combined with clavulanate against susceptible MDR-TB and XDR-TB strains.[142,143] Reports of successful treatment of tuberculosis with β-lactams have been sporadic. In a study of 31 patients, meropenem-clavulanate was added to a linezolid-containing regimen for treating MDR-TB/XDR-TB. The patients receiving meropenem-clavulanate had a higher percentage of smear and culture conversion than patients who did not.[143] However, activity of β-lactam agents against intracellular mycobacteria is generally poor.[144,145] In concentrations of 50 μg/mL in a macrophage model, ceforanide, active in vitro, was unable to inhibit tubercle bacilli.

Amithiozone

Amithiozone (thiacetazone), a thiosemicarbazole, is active against many strains of *M. tuberculosis*.[20] Because of its low cost, amithiozone has been employed as a first-line drug, particularly in East Africa.[20] However, because of severe toxicity in HIV-infected recipients there, clinical usage no longer seems appropriate.[13]

New Drugs for Tuberculosis

This is an era of unprecedented interest and activity in the development of new antituberculous drugs. At the present time there are more than 15 new compounds with potential antituberculosis activity in preclinical or clinical phases of development. Approximately twice that number of other interesting molecules have been identified in screening, lead identification, or lead optimization.

The diarylquinoline bedaquiline (also referred to as TMC207 or Sirturo) (see Fig. 39.1) is a novel compound that acts by inhibiting the *M. tuberculosis* adenosine triphosphate synthase, becoming bactericidal over several days.[146,147] Bedaquiline oral absorption is doubled in the fed versus the fasting state.[148] The drug is metabolized by the liver, largely by CYP3A4, with negligible renal excretion. The tertiary amino group is progressively demethylated, with the *N*-monodesmethyl compound M2 having reduced antibacterial effect (about fivefold less). The ratio of plasma metabolite, M2, to bedaquiline is 0.25:0.30. The mean terminal half-life of bedaquiline with one dosing regimen was 164 days (range, 62–408 days), and the mean terminal half-life of M2 was 159 days (range, 69–407 days).[149] Protein binding of both compounds is greater than 99%, with little CSF penetration anticipated. Clinical studies with 100-mg tablets have begun with a 2-week loading period of 400 mg once a day, followed by three times a week of 200 mg, with food, up to a total duration of 24 weeks. After loading, doses of 200 mg should be at least 2 days apart. Rifampin reduces bedaquiline levels by 52% and M2 levels by 25%. Lopinavir-ritonavir approximately doubles bedaquiline exposure. Both bedaquiline and M2 cause QT-interval prolongation, which could be a potential lethal toxicity in patients with hypokalemia, in the presence of other drugs that prolong the QT interval such as fluoroquinolones or clofazimine, or when drug interactions increase bedaquiline exposure. Nausea is another side effect. No effect on bedaquiline pharmacokinetics was observed with coadministration of INH, ethambutol, cycloserine, ofloxacin, kanamycin, pyrazinamide, or efavirenz.[148,150]

Bedaquiline demonstrates significant in vitro potency against *M. tuberculosis*—both drug-susceptible and multidrug-resistant strains—as well as multiple other mycobacteria.[146] Animal studies suggested that bedaquiline has significant potential to shorten treatment duration for both drug-susceptible and drug-resistant strains.[151] In initial and follow-up reports of a randomized trial of bedaquiline versus placebo in multidrug regimens for patients with newly diagnosed MDR-TB disease, the patients receiving bedaquiline had significantly reduced time to sputum conversion with an increased proportion of patients with sputum conversion. Bedaquiline also prevented resistance against companion drugs in the course of treatment.[152,153] One caveat that emerged from data filed with the FDA is that in a larger cohort of patients the bedaquiline treatment arm was associated with five times the number of deaths compared with the placebo arm.[154] Investigation of these deaths showed that half of them were due to progressive tuberculosis and that to date there is no direct pathophysiologic link between bedaquiline and the other deaths. The FDA approved bedaquiline for treatment of drug-resistant tuberculosis with a black box warning relating to possible cardiac toxicity and sudden death. Subsequent analyses have failed to show a significant risk of cardiac toxicity with long-term bedaquiline use.[150] As with the quinolones, a risk-benefit analysis is necessary for any patient to receive bedaquiline, but it would seem difficult to withhold bedaquiline to patients with few other antibiotic choices even in the presence of a prolonged QT interval on an electrocardiogram.

OPC-67683, or delamanid (see Fig. 39.1), is a new agent derived from the nitro-dihydro-imidazooxazole class of compounds that inhibits mycolic acid synthesis and has shown potent in vitro and in vivo activity against both drug-susceptible and drug-resistant *M. tuberculosis* strains.[155,156] Delamanid is a prodrug that is converted to the active compound by the mycobacterial cell. The drug is insoluble in water and compounded in 5% gum arabic to facilitate absorption from the gastrointestinal tract. Delamanid is highly protein bound and principally metabolized by a chemical reaction with serum albumin, with little hepatic or renal excretion of native drug.[157] Drug interactions with cytochrome enzymes are thought to be minimal. The most common side effects are nausea, vomiting, and dizziness. In one assessment of early bactericidal activity of delamanid in patients with tuberculosis, doses of 200 mg and 300 mg daily resulted in decreased sputum *M. tuberculosis* burden of a magnitude similar to that of rifampin.[158] In a placebo-controlled trial of delamanid, dosages of 100 mg/day or 200 mg/day administered over 2 months as part of a multidrug regimen for MDR-TB were associated with a significant increase in sputum-culture conversion at 2 months.[159] Most adverse events were mild to moderate in severity and were evenly distributed across groups. QT-interval prolongation was reported significantly more frequently in the groups that received delamanid. Delamanid has also been given safely in combination with bedaquiline. The European Medicines Agency conditionally approved delamanid (Deltyba) for MDR-TB at an adult dosage of two 50-mg tablets, orally twice a day with food.

PA-824, or pretomanid, is a nitroimidazole that has undergone extensive testing in animal models and is currently being studied primarily in patients with MDR-TB.[159,160,161,162] The mechanism of action of delamanid and of PA-824 is not yet known, but both appear to generate radicals with toxic effects on mycolic acids and protein biosynthesis.[163] PA-824 is potent in vitro against drug-susceptible and drug-resistant tuberculosis strains and appears to have activity against nonreplicating or slowly replicating strains. Initial dose-ranging monotherapy studies have shown dose-related early bactericidal activity.[159] An initial clinical study in drug-susceptible tuberculosis demonstrated that the combination of PA-824, moxifloxacin, and PZA had antituberculosis activity in sputum lasting 14 days, comparable with that of the current standard regimen for drug-susceptible tuberculosis.[162] A phase II trial of moxifloxacin, pretomanid, and pyrazinamide as the first 8 weeks of treatment of drug-susceptible and drug-resistant tuberculosis found this regimen well tolerated and superior in bactericidal activity compared with a standard tuberculosis regimen (in patients with drug-susceptible disease).[164] An important implication is that this regimen is effective and does not contain rifampin, and thus there is a low interaction potential with antiretroviral regimens. PA-824 would also be suitable for MDR-TB isolates. Trials involving longer duration of PA-824 administration are ongoing.

WORLD HEALTH ORGANIZATION ANTITUBERCULOSIS DRUG CLASSIFICATION FOR DRUG-RESISTANT TUBERCULOSIS

Core antituberculosis medications for MDR-TB and XDR-TB are grouped by the WHO in categories A through D with subgroups D-1, D-2,

and D-3.[10] Group A drugs include later-generation fluoroquinolones (levofloxacin, moxifloxacin, and gatifloxacin). Group B drugs include second-line injectable agents (amikacin, capreomycin, kanamycin, and streptomycin). Group C includes other core second-line agents listed in order of decreasing usual preference (ethionamide-prothionamide, cycloserine-terizidone, linezolid, and clofazimine). Other drugs that may be used are included in group D, add-on agents that are noted to be "not part of the core MDR-TB regimen" (subgroup D-1 includes PZA and ethambutol; subgroup D-2 includes bedaquiline and delamanid; and subgroup D-3 includes PAS, imipenem-cilastatin, and meropenem). Both carbapenems must be given with amoxicillin-clavulanate, as clavulanic acid is needed for efficacy of the carbapenem against *M. tuberculosis*.

Given the toxicity and relative weakness of the traditional second-line drugs, ethionamide, cycloserine, and PAS, we believe contemporary regimens for treating MDR-TB and XDR-TB should include newer agents in their place. A recent MDR Survival Guide notes the importance of linezolid and clofazimine in the treatment of MDR-TB, with mounting evidence for the efficacy and tolerability of bedaquiline and delamanid.[14]

THERAPEUTIC DRUG MONITORING

The role of therapeutic drug monitoring (TDM) remains controversial, especially in the routine management of most patients with tuberculosis. As pointed out in the most recent ATS/CDC/IDSA guidelines on tuberculosis therapy, "TDM cannot predict who will be cured, fail or relapse; however, it does allow for timely, informed decisions regarding the need for dose adjustment when necessary."[19] For some antituberculosis drugs such as amikacin and cycloserine, TDM is essential for minimizing risk of drug toxicity. It is hoped that prospective studies will be undertaken to better define the role of TDM in tuberculosis management.

COADMINISTRATION OF ANTITUBERCULOSIS THERAPY AND HUMAN IMMUNODEFICIENCY VIRUS MEDICATIONS

The most recent ATS/CDC/IDSA tuberculosis treatment guidelines note that available data show significant reductions in mortality and AIDS-defining illnesses when patients with HIV infection and tuberculosis receive ART in conjunction with daily antituberculosis medications.[19] A meta-analysis reported in this document identified no increase in the risk of other adverse events or poor outcome of tuberculosis therapy. Therefore it was recommended that patients with tuberculosis and HIV infection receive ART during antituberculosis treatment. ART should ideally be started within 2 weeks for patients with $CD4^+$ count <50 cells/mm^3 and by 8 to 12 weeks for patients with $CD4^+$ count ≥50 cells/mm^3.

MAJOR DRUGS FOR TREATMENT OF NONTUBERCULOUS MYCOBACTERIAL INFECTIONS (see Chapters 251 and 252)

NTM vary greatly in susceptibility to antimicrobial agents.[165–167,168] Some such as *M. kansasii* are susceptible to agents used principally for the treatment of tuberculosis; others such as *M. fortuitum* and *M. chelonae* respond to antibiotics used more commonly for pyogenic bacterial infections; still others including MAC, *M. abscessus* subsp., *M. simiae,* and many others are broadly resistant. The role of NTM susceptibility testing has been progressively better defined by the publication of national guidelines for testing by the Clinical Laboratory Standards Institute in 2003, 2011, and 2017.[169,170,209] Hence the indications, feasibility, and limitations of chemotherapy for NTM infections based on susceptibility results are available for many species. An important example of that process is MAC, where susceptibility testing has limited clinically predictive value except for the newer macrolides and amikacin.[168]

Macrolides (see Chapter 29)

Antimicrobial Activity and Resistance

Pretreatment strains of *M. kansasii, M. marinum, M. haemophilum, M. malmoense,* MAC, *M. chelonae,* and *M. abscessus* subsp. *massiliense* are susceptible to achievable therapeutic concentrations of the newer macrolides clarithromycin and azithromycin. This has resulted in a dramatic change in therapy for NTM infections, with a macrolide now part of the treatment regimen for many species.[171–175] These agents are especially efficacious against both pulmonary and disseminated MAC infections.[168,176,177] Both macrolides have proved efficacious for prevention of disseminated MAC infection in patients with AIDS.[178,179] Although some NTM such as *M. fortuitum*, *M. abscessus* subsp. *abscessus,* and *M. abscessus* subsp. *bolletii* may appear to be susceptible to macrolides on routine evaluation, they contain an inducible macrolide resistance gene that becomes apparent and confers macrolide resistance after macrolide exposure either in vitro or in vivo.[180] This intrinsic resistance mechanism is mediated by a series of chromosomal *erm* (erythromycin methylase) genes found in *M. tuberculosis, M. fortuitum, M. abscessus* subsp. *abscessus,* and *M. abscessus* subsp. *bolletii*.[180] This resistance mechanism is not found in the slowly growing NTM species.

Macrolides should not be used as monotherapy for any macrolide-susceptible NTM because of the rapid emergence of acquired mutational resistance, which results from a point mutation at adenine 2058 or 2059 on the 23S ribosomal RNA gene, the presumed macrolide-binding site, and produces cross-resistance to all macrolides.[181,182] The emergence of this type of resistance is inevitably associated with treatment failure and increased mortality.[183,184] Risk factors other than macrolide monotherapy include a lack of adequate companion medications to protect against the emergence of macrolide resistance, especially the combination of macrolide and quinolone without other medications.

Pharmacology

Clarithromycin is metabolized in the liver, and significant concentrations of the 14-OH metabolite are detectable in the serum.[185] Clarithromycin is also excreted in part by the kidneys, and a reduction in dosage is required in elderly patients, patients with low body weight, and patients with reduced renal function.

Adverse Reactions

The most common side effects are nausea, vomiting, and diarrhea, which are generally dose related.[186] Toxic hepatitis occurs with daily doses greater than 1.0 g and is associated with elevated levels of alkaline phosphatase and γ-glutamyltransferase.[186] Temporary hearing loss may also occur with high doses of azithromycin.[187]

Significant Drug Interactions

Clarithromycin is metabolized by the cytochrome P-450 enzyme system, and serum levels are dramatically reduced by enzyme inducers such as rifampin.[185] Clarithromycin is an inhibitor of the P-450 enzyme system, and its use results in increased serum levels and potential increased toxicities of multiple drugs metabolized by these enzymes including rifabutin, carbamazepine, cisapride, astemizole, terfenadine, and theophylline.[86,87] Clarithromycin inhibits the metabolism of PIs as well. In contrast, azithromycin is not metabolized by the cytochrome P-450 system and has no significant drug interactions.[187]

Dosage

The usual daily therapeutic doses are 500 mg twice daily for clarithromycin and 250 mg once daily for azithromycin. The usual therapeutic doses for intermittent, three-times-weekly dosing are 1000 mg (500 mg twice a day) for clarithromycin and 500 mg for azithromycin. For noncavitary MAC lung disease, the usual clarithromycin dosage is three times weekly with 500 mg in the morning and evening; for azithromycin, the dosage is 500 mg given three times weekly. For disseminated MAC prophylaxis, the dosage of azithromycin is 1200 mg once a week.[179]

Rifampin

Antimicrobial Activity

Rifampin is employed for the treatment of many slowly growing NTM infections. In vitro, all untreated strains of *M. kansasii, M. marinum, M. haemophilum,* and *M. xenopi* are inhibited by 0.25 to 1.0 μg/mL.[168,188,189] Other species are much less susceptible. Only one-half of

MAC strains are inhibited in vitro by 4 to 16 μg/mL of rifampin. Synergy between rifampin and other agents has been demonstrable for a number of species in vitro. Its role as a single agent is discouraged because resistance will occur.[189]

Pharmacology, Adverse Events, and Significant Drug Interactions

See the earlier discussion in "Rifampin" under "First-Line Antituberculous Drugs."

Usage

The excellent response of *M. kansasii* infections to rifampin-containing regimens has made rifampin the basis of most treatment regimens.[168] Rifampin doses are the same as those for treatment of tuberculosis. For patients with HIV infection receiving PIs or NNRTIs, rifabutin (300 mg three times per week) is recommended over rifampin[168] because of its lesser effect on the cytochrome P-450 system. The role of rifampin in the treatment of MAC disease is less clear. The apparent benefit of rifampin in multidrug MAC treatment regimens is protection against the emergence of acquired mutational macrolide resistance not due to direct antimycobacterial activity.

Rifabutin

Antimicrobial Activity

Rifabutin is inhibitory against 90% of strains of MAC at a concentration of 2 μg/mL.[83,84] It is concentrated several-fold in tissue and, similar to rifampin, has gastrointestinal toxicity as its most common adverse effect. Rifabutin at a dosage of 300 mg/day has been shown to reduce by 50% the incidence and rate of dissemination of MAC infections in patients with AIDS with $CD4^+$ counts <200 cells/mm^3,[190] although it is probably not as effective as the newer macrolides.

Pharmacology, Adverse Events, and Significant Drug Interactions

The reader is referred to the earlier discussion in "Rifabutin" under "First-Line Antituberculous Drugs."

Usage

Rifabutin is used in place of rifampin in HIV-infected patients receiving PIs and NNRTIs, although it is not recommended with saquinavir or delavirdine.[13] Rifabutin is also an effective prophylaxis agent against disseminated MAC. However, for therapy of disseminated disease in patients with AIDS, a placebo-controlled study showed that through 16 weeks of follow-up, a dose of 300 mg daily did not increase the culture conversion rate over clarithromycin and ethambutol alone, but it did protect against the development of macrolide resistance.[191] Rifabutin was frequently used in multidrug treatment of MAC lung disease in the past but because of poor tolerability was replaced by rifampin in most circumstances. There are no published studies comparing the efficacy of rifabutin versus rifampin in treatment regimens for MAC, although there are theoretical reasons to believe that rifabutin would be more efficacious than rifampin. Rifabutin is more clearly an important element in MAC treatment regimens in patients who have failed a regimen containing rifampin or who have developed macrolide resistance.[168]

Aminoglycosides

Aminoglycoside antibiotics have been used extensively for the treatment of rapidly growing as well as some slow-growing NTM infections. Among *M. kansasii* strains, 86% demonstrated streptomycin susceptibility. Of strains of MAC, 44% have been found to be susceptible to streptomycin. Rapidly growing mycobacteria, including *M. fortuitum* and *M. abscessus,* are resistant to streptomycin.

Amikacin is the most active aminoglycoside against NTM.[168,192–194] However, marked variability exists between mycobacterial species in susceptibility. All strains of *M. marinum, M. kansasii,* and *M. fortuitum* are susceptible to 4 μg/mL or less,[188,193,194] whereas isolates of *M. chelonae, M. abscessus,* and MAC are more resistant but are usually inhibited by 8 to 64 μg/mL of amikacin.[193,194] Doses for streptomycin and amikacin are generally the same as those for treatment of tuberculosis. Tobramycin is the most active aminoglycoside for treatment of *M. chelonae* and is the recommended aminoglycoside for that organism.[193,194] Mutational resistance to amikacin due to a 16S ribosomal RNA gene mutation can occur with MAC therapy and is associated with amikacin MICs greater than 64 μg/mL.[195] Aside from macrolides, amikacin is the only antimicrobial with a demonstrated association between the MIC for MAC and treatment response. Also similar to the macrolides, this possibility of acquired mutational resistance emphasizes the importance of combining amikacin with adequate companion medications to prevent this occurrence. Resistance with amikacin therapy has also been described with *M. abscessus*.[196]

Amikacin (generic) has also been administered by inhalation for treatment of NTM lung disease, especially MAC lung disease. However, despite widespread use, there are very few data supporting inhalational use. An amikacin sulfate preparation encapsulated in liposomes for inhalational delivery has been tested for MAC lung disease. A placebo-controlled phase 2 trial in patients with treatment-refractory MAC lung disease showed that the inhaled liposomal amikacin compound combined with guideline-based therapy achieved early and sustained negative sputum cultures in treatment-refractory MAC lung disease significantly better than guidelines-based therapy alone.[197] Initial results of a phase 3 randomized, open-label study of the liposomal amikacin preparation in adults with treatment-refractory MAC lung disease have shown similarly favorable results.[198]

Ethambutol

Ethambutol has good in vivo activity against *M. kansasii* and to a lesser extent MAC and is included as part of treatment regimens for these organisms.[168] Although MICs for ethambutol with MAC isolates are high compared with *M. tuberculosis,* ethambutol is unquestionably the critical element in preventing the emergence of acquired mutational macrolide resistance and must be included in MAC treatment regimens for the purpose of preventing the emergence of macrolide resistance regardless of the ethambutol MIC. It also has activity against most other slowly growing NTM including *M. kansasii, M. marinum,* and *M. xenopi.* Species of rapidly growing mycobacteria are all highly resistant with the exception of the *M. smegmatis.*

LESS FREQUENTLY USED MISCELLANEOUS ANTIMICROBIAL AGENTS FOR TREATMENT OF NONTUBERCULOUS MYCOBACTERIA

Isoniazid

Drugs such as INH used principally for treatment of *M. tuberculosis* were evaluated relatively early for their activity against NTM. INH inhibits nearly 90% of strains of *M. kansasii* at concentrations of 1 to 5 μg/mL, as contrasted to only 10% to 30% of MAC strains. At the present time INH is included routinely in the therapy for *M. kansasii* in the United States, although it has largely been replaced by macrolide for this organism.[168] INH is also used for *M. xenopi* and *M. szulgai,* but also is frequently replaced by macrolide. It is not currently recommended for treatment of MAC.

Tetracyclines

Approximately 50% of isolates of the rapidly growing species *M. fortuitum* and 20% of *M. chelonae* are susceptible to tetracycline.[195] Minocycline and doxycycline are twofold to fourfold more active than tetracycline[194] and have been effective in therapy when the isolates were susceptible in vitro.[145] Minocycline and doxycycline are also active against *M. marinum*[182,199,200] and have been used successfully in *M. marinum* infections.[168,199] A parenteral tetracycline, tigecycline, with activity against all rapidly growing mycobacteria has been marketed. It is frequently used as part of combination therapy for *M. abscessus* lung disease; however, few data evaluating its efficacy in this role are available.[201] Tigecycline is also associated with frequent and severe side effects, most notably nausea and vomiting.

Sulfonamides

Sulfamethoxazole is active against *M. fortuitum* but not against *M. chelonae* or *M. abscessus*.[193,194] Localized infections have been cured with sulfamethoxazole alone or in combination with trimethoprim.[145]

M. marinum infections have responded to therapy with trimethoprim-sulfamethoxazole,[168] but strains are susceptible in vitro only against a low inoculum.[175]

Both *M. marinum* and *M. kansasii* exhibit very similar drug susceptibilities. Sulfamethoxazole is also active against isolates of *M. kansasii.* It has been curative in combination regimens used for treatment of rifampin-resistant *M. kansasii* infections.[189]

Limited experience indicates some in vitro activity and clinical efficacy of sulfonamides against *M. terrae* complex, *M. haemophilum, M. simiae,* and MAC.[168]

Quinolones

The newer fluorinated quinolones (ciprofloxacin, moxifloxacin, levofloxacin) have in vitro activity against a number of NTM at achievable serum levels.[194,202] *M. fortuitum* strains are the most susceptible, with ciprofloxacin MICs of 0.25 µg/mL or less and good responses clinically.[202] More recent studies have shown levofloxacin to have comparable activity to ciprofloxacin, whereas the newer quinolone moxifloxacin has twofold to fourfold lower MICs than these older agents.[203] A number of species are inhibited by intermediate concentrations of ciprofloxacin (1–4 µg/mL). These include *M. chelonae* (25%), *M. malmoense, M. marinum, M. xenopi, M. kansasii, M. haemophilum,* and some strains of MAC. The newer quinolones gatifloxacin and moxifloxacin are more active than ciprofloxacin.[203] The clinical efficacy of the quinolones for these species has yet to be established due to the lack of in vivo evidence correlating favorable MICs, especially for MAC, with favorable treatment outcomes. There is also a clear risk for developing acquired mutational macrolide resistance for MAC with the combination of macrolide and fluoroquinolone without other companion medications such as ethambutol.[204,205] For other organisms with a clearer correlation between in vitro susceptibility and treatment outcome, resistance to ciprofloxacin after monotherapy has been described and presumably involves the same DNA gyrase mutations observed with quinolone resistance with *M. tuberculosis.*[113]

Linezolid

More recent studies have shown that many NTM are inhibited by 8 µg/mL (susceptible MICs) of linezolid including *M. fortuitum, M. kansasii, M. marinum,* and *M. haemophilum.* Isolates of *M. chelonae* all are susceptible or intermediate to linezolid, and in vitro it is the most active oral drug available for this species after the macrolides. Some isolates of *M. abscessus* subsp. show susceptible MIC levels, which is especially important for these species, for which there are limited choices for oral drugs to include in treatment regimens. Isolates of MAC and *M. simiae* are usually resistant to linezolid.[207]

β-Lactams

All mycobacteria produce β-lactamase, although it can be difficult to detect in MAC. However, β-lactams or combinations of β-lactam and β-lactamase inhibitors have been shown to be active or useful clinically only for the *M. fortuitum* complex. Cefoxitin, cefmetazole, and imipenem-cilastatin are active in vitro against approximately 80% of *M. fortuitum* strains and most isolates of *M. abscessus* subsp. at clinically achievable plasma concentrations.[135,208]

Clofazimine

Discussed more fully in "Drugs for Treatment of Hansen Disease (Leprosy)," clofazimine (Lamprene) possesses in vitro activity against *M. chelonae, M. abscessus,* and MAC. Most strains are inhibited by 1.6 to 2.0 µg/mL.[168] Clinical experience with clofazimine in therapy against MAC in AIDS was disappointing.[168] Clinical experience with MAC lung disease has been infrequently reported, although it is frequently used for this indication. More recent reports suggest that it is generally well tolerated, but its role in MAC treatment regimens is still unclear. At the present time it appears to be similar to rifampin in that it helps protect against the emergence of acquired mutational macrolide resistance.

Susceptibility Tests

Standardized methods for susceptibility testing of NTM were approved for the first time in 2003 by the Clinical Laboratory Standards Institute and subsequently updated.[145] In vitro susceptibility of NTM drugs is no guarantee of therapeutic efficacy. Previously cited failures of fluoroquinolones and ethambutol in MAC infections indicate limitations in extrapolating in vitro data to clinical experience. As a rule, favorable therapeutic results are likely when drugs to which NTM are susceptible in vitro are used, and poor outcomes can be anticipated when there is in vitro resistance. Least predictable are outcomes of MAC infections, for which routine susceptibility testing is *not* recommended except for clarithromycin (or azithromycin).[145,146,168]

DRUGS FOR TREATMENT OF HANSEN DISEASE (LEPROSY)

(see Chapter 250)

Background

The special parasite-host relationship of *M. leprae* (Hansen bacillus), characterized by persistence of the organism in tissue for years, has mandated prolonged chemotherapy to prevent relapse. For years, chemotherapy for leprosy mainly consisted of dapsone alone, which produced gratifying clinical results and was affordable. However, because of self-supervised monotherapy, resistance of leprosy bacilli, both secondary and now primary, became a problem worldwide.[210] At the present time multidrug therapy is the rule for both multibacillary and paucibacillary disease, and this approach has markedly increased cure rates and decreased the incidence of drug resistance. The principal agents used in therapeutic multidrug regimens are dapsone, rifampin, and clofazimine.

Dapsone

Derivation and Structure

Dapsone (4,4′-diaminophenyl sulfone), a synthetic compound, was demonstrated to be effective in rat leprosy in 1941 and soon thereafter was used successfully in human trials.

Mechanism of Action

Sulfones inhibit bacterial dihydropteroate synthase, as do sulfonamides, and presumably inhibit *M. leprae* by the same mechanism.

Antimicrobial Activity

By mouse foot pad inoculation, 0.003 µg/mL of dapsone is estimated to inhibit multiplication of *M. leprae.* Dapsone has been described as "weakly bactericidal" for susceptible leprosy bacilli. In humans, it has been estimated that 99.9% of bacillary populations are killed after 3 to 4 months of dapsone therapy.[211] In lepromatous (multibacillary) patients on monotherapy, secondary dapsone resistance often emerges 5 to 24 years after beginning therapy.[212] Before the usage of current standard multidrug regimens, secondary resistance occurred in approximately 20% of cases.

Pharmacology

Dapsone is well absorbed orally. Distributed throughout body fluids, tissue concentrations are approximately 2 µg/mL. The plasma half-life of dapsone is 21 to 44 hours, with some drug retention for up to 3 weeks. Dapsone becomes acetylated with 70% to 80% excreted as metabolites in urine. The dosage should be reduced accordingly in renal failure.

Adverse Reactions

An oxidant drug, dapsone produces dose-dependent hemolysis, which is not of clinical consequence in patients without a hematologic disorder taking dapsone 50 to 100 mg daily. Hemolysis is greatly enhanced in patients with glucose-6-phosphate dehydrogenase deficiency, especially in its severe forms. Gastrointestinal intolerance occurs with resulting anorexia, nausea, or vomiting. Hematuria, fever, pruritus, rashes, and granulocytopenia can occur.

Dapsone is now being used in patients with AIDS as prophylaxis and treatment of *Pneumocystis jirovecii* pneumonia. These patients usually have preexisting anemia, making dapsone-induced hemolysis less well tolerated. Conversion of up to 20% of erythrocyte hemoglobin to methemoglobin can occur with dapsone doses of 100 mg daily. Although methemoglobinemia is usually asymptomatic, it may

become of clinical concern if the patient develops hypoxemia from lung disease. Rash is common in this patient population. In one study using dapsone, 100 mg daily, for prophylaxis, 33 of 47 patients discontinued the drug.[213]

In patients with leprosy, reactions with dapsone may be difficult to extricate from the reactions associated with the disease itself.[214] A sulfone syndrome occurring 5 to 6 weeks after the initiation of therapy can be characterized by fever, jaundice, dermatitis, and lymphadenopathy—a presentation similar to infectious mononucleosis.[215] During initial dapsone therapy, erythema nodosum leprosum reactions commonly become manifest in patients with multibacillary disease.

Usage

Dapsone and rifampin are the principal therapeutic agents for the treatment of both multibacillary and paucibacillary *M. leprae* infections. Usage in prophylaxis or treatment of *P. jirovecii* pneumonia is discussed in Chapter 269. Dapsone is also useful in dermatitis herpetiformis, but that is beyond the scope of this chapter.

Availability and Dosage

Dapsone is available generically in tablets of 25 or 100 mg. The daily dose for adults is 100 mg and for children is 1.0 to 1.5 mg/kg/day. The WHO recommends administration daily for 6 months for paucibacillary disease and treatment for 1 year for multibacillary disease. The National Hansen's Disease Program (NHDP) recommends 1 year of treatment for paucibacillary disease and a minimum 2 years of treatment for multibacillary disease.

Rifampin

Mechanism of Action and Resistance

The mechanism of action of rifampin is presumed to be inhibition of *M. leprae* DNA-dependent RNA polymerase that produces a relatively rapid bactericidal effect. Its inhibitory concentration of human strains of *M. leprae* tested in mice is 0.3 μg/mL. Acquired rifampin resistance is caused by mutational changes in RNA polymerase.[216]

Usage

Clinical usage of rifampin has confirmed that it is more bactericidal by several orders of magnitude than all other antileprosy drugs either alone or in combination. It is considered the only rapidly bactericidal drug against *M. leprae*. Using a skin biopsy assay, a single 1500-mg dose of rifampin was determined to reduce the viability of leprosy bacilli to undetectable levels by 3 to 5 days.[217] Despite such a dramatic impact on numbers of tissue *M. leprae* organisms, rifampin must be employed with one or more companion drugs to prevent the development of resistance.[211] The high cost of rifampin has discouraged daily usage in economically disadvantaged regions. However, once-monthly therapy with 600 to 1200 mg of rifampin in combination drug regimens has produced satisfactory clinical responses with a minimum of adverse reactions.[218] Current recommendations are that rifampin should be administered in a single monthly supervised dose of 600 mg. This dosage is continued for 6 months in paucibacillary disease and for a minimum of 2 years in multibacillary disease. In the United States, rifampin is given as a 600-mg daily dose in both of the settings described. Reversal and erythema nodosum leprosum reactions with rifampin have been comparable or less severe than with sulfones alone. Daily rifampin treatment may reduce both the serum levels and subsequently the beneficial effects of corticosteroids for reactions by inducing hepatic microsomal enzymes. In patients with reactions requiring steroids, switching rifampin dose from daily to monthly helps to overcome interaction between rifampin and corticosteroids.

Clofazimine (Lamprene)

Derivation and Structure

Clofazimine is a phenazine dye.

Mechanism of Action and Antimicrobial Activity

The precise mechanism of action of clofazimine is unknown. Highly lipophilic and bound to mycobacterial DNA, clofazimine is weakly bactericidal against *M. leprae*. Its action may relate to iron chelation with resulting production of nascent oxygen radicals intracellularly.[219] The inhibitory concentration of clofazimine in mouse tissue is between 0.10 mg/kg and 1.0 mg/kg. A delay of about 50 days ensues before tissue antimicrobial activity can be demonstrated in humans.

Clofazimine is not commercially available in the United States; it is distributed through the NHDP. NHDP holds the Investigational New Drug (IND) application for treatment of leprosy in the United States. To obtain clofazimine, physicians are required to register as an investigator under the NHDP IND. This requires submitting a curriculum vitae and a signed FDA form 1572 to the NHDP. For further information or to request investigator status, physicians should contact the NHDP at 1-800-642-2477 or nhdped@hrsa.gov or go to http://www.hrsa.gov/hansensdisease/index.html.

Pharmacology

Clofazimine pharmacokinetics are complex. Absorption is quite variable, with 9% to 74% of an administered dose appearing in feces. Oral administration results in plasma concentrations of 0.4 to 3 μg/mL with a half-life of approximately 70 days. Clofazimine is widely distributed throughout reticuloendothelial tissues, especially liver, spleen, lung, adrenals, adipose tissue, and skin lesions. Red-orange phagocytized crystals of clofazimine are observed microscopically in macrophages. It is largely unmetabolized and subsequently slowly excreted with less than 1% in urine. Biliary excretion appears to be the major route of excretion. Excretion also occurs in breast milk. Dosage of 100 mg/day has been calculated to result eventually in a total accumulation of at least 10 g in human tissue.

Adverse Reactions

Gastrointestinal intolerance (anorexia, diarrhea, abdominal pain) is the most common therapy-limiting side effect and is generally dose related. Dry mouth and dry skin may occur. Skin pigmentation is quite common, resulting from drug accumulation and producing red-brown to nearly black discoloration, especially in dark-skinned people. Skin discoloration is reversible but may take several months to years after discontinuation of medication. Avoidance of direct sun exposure and use of sun block before sun exposure are recommended. Suicidal ideation (rare) has been reported with skin discoloration. Prolongation of QT interval associated with torsades de pointes has been reported in patients taking >100 mg daily and other QT interval–prolonging drugs.

Usage

The current role of clofazimine is principally in combination with rifampin and dapsone for multibacillary disease. It is also used in combination for sulfone-resistant infections and for individuals who are intolerant to sulfones, usually because of severe sulfone-associated erythema nodosum leprosum or reversal reactions. Such reactions occur much less often with clofazimine than with dapsone[220] possibly because of antiinflammatory properties of clofazimine.

Availability and Dosage

Clofazimine is supplied in 50-mg capsules. For multibacillary disease, it is administered in a dosage of 50 mg/day for a minimum of 2 years in combination with rifampin and dapsone. When used as a dapsone alternative, dosage has usually been 100 to 300 mg/day.

Additional or Second-Line Drugs

Thiacetazone (Amithiozone)

Efficacy of thiacetazone is greater in tuberculoid (paucibacillary) than in lepromatous (multibacillary) disease. It can be administered when sulfones are not tolerated. Considerable cross-resistance occurs with sulfones. Thiacetazone is unavailable in the United States.

Ethionamide and Protionamide

Ethionamide (Trecator-SC) is described in "Second-Line Antituberculous Drugs." Pharmacokinetics and dosing are similar for ethionamide and its congener protionamide (which is unavailable in the United States), and these agents provide alternatives to clofazimine in multidrug regimens for multibacillary disease in patients who are unable to tolerate

clofazimine or refuse it because of skin pigmentation. Ethionamide and protionamide are apparently weakly bactericidal against *M. leprae*. Ethionamide is provided in 250-mg tablets. The usual dosage is 250 mg daily. Both agents are expensive and cause considerable gastrointestinal intolerance and occasional hepatitis.

Other Substituted Rifamycins

Rifabutin (Mycobutin) and rifapentine (Priftin) are substituted rifamycins that are active against *M. leprae*. Both are approved by the FDA for treatment of tuberculosis. In mice, these compounds are even more active than rifampin,[221] which raises interest in their use, especially in intermittent regimens.

Other Sulfones

Acedapsone

Acedapsone (4,4′-diacetyldiaminodiphenyl sulfone) is a long-acting intramuscular repository derivative of dapsone. The parent compound possesses little activity against *M. leprae* but is metabolized into active dapsone. Its half-life is 46 days, and the half-life of the derived dapsone is 43 days.[4,222] A 300-mg intramuscular dose maintains dapsone levels in volunteers above the inhibitory concentration for *M. leprae* for approximately 100 days. Microbiologic and clinical responses are slower than those for daily dapsone. Long-term studies with acedapsone by injection five times yearly have yielded encouraging results. Acedapsone shows promise especially in regions where, or in patients in whom, long-term oral therapy is not practical.

Sulfoxone

Less well absorbed and more expensive than dapsone, sulfoxone, a disubstituted sulfone, may be better tolerated gastrointestinally. It is formulated in 165-mg enteric-coated tablets, with a usual daily dosage of 300 mg.[222]

Newer Agents

Several other agents have shown promising activity against *M. leprae* in mouse foot pad models and early clinical trials. These agents include minocycline (Minocin)[223]; clarithromycin (Biaxin)[223]; and fluorinated quinolones pefloxacin, ofloxacin (Floxin),[224] and especially sparfloxacin.[225] Their roles in replacing drugs in existing multidrug regimens remain to be determined, although none of these agents appears to be as bactericidal against *M. leprae* as rifampin, and neither pefloxacin nor sparfloxacin is on the market. Current efforts with these newer agents are also focusing on short-course therapy,[226] rather than the current standard 2-year regimens.

Chemotherapy-Associated Reactions in Leprosy

Febrile reactions in leprosy can be ameliorated with a conventional dosage of acetylsalicylic acid (aspirin). Immunologic reactions are common during chemotherapy. Reversal reactions associated with swelling and edema in preexisting skin lesions or peripheral neuropathy in more severe reactions usually occur in the first year of therapy. Corticosteroids such as prednisone, 40 to 80 mg/day initially with subsequent tapering of dosage, have been reasonably efficacious for reversal reactions. Thalidomide is not used for reversal reactions.

For patients with erythema nodosum leprosum reactions, thalidomide in an initial dosage of 100 mg four times a day is the treatment of choice. Its beneficial effect for these reactions appears to be mediated by the inhibition of tumor necrosis factor-α.[227] Treatment is initiated at 400 mg/day to attain control of the disease but should then be tapered over the first week with a maintenance dose of 50 to 100 mg/day. Thalidomide is commercially available for the treatment of leprosy, but its usage is tightly regulated (see Chapter 250). Because of its marked teratogenicity, thalidomide should never be administered to women of childbearing potential. In patients with erythema nodosum leprosum for whom thalidomide is unacceptable, high-dose prednisone is an alternative treatment. Patients who manifest puzzling or severe reactions are best managed by HD specialists such as those at the National Hansen's Disease (Leprosy) Clinical Center, Baton Rouge, Louisiana. The NHDP located in Baton Rouge is the only facility in the United States devoted to diagnosis, treatment, and research concerning HD.

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40A Antifungal Agents: Amphotericin B

David A. Stevens

GENERAL FEATURES

Mechanism of Action

Amphotericin B is available in a formulation with deoxycholate and in lipid-associated formulations. For all preparations, the active component is amphotericin B produced by *Streptomyces nodosus*. Amphotericin B is a lipophilic molecule (Fig. 40A.1) that exerts its antifungal effect by insertion into the fungal cytoplasmic membrane, probably orienting as head-to-tail oligomers perpendicular to the plane of the membrane.[1] The drug is closely bound to sterols such as ergosterol. Amphotericin B causes membrane permeability to increase. At lower drug concentrations, potassium ion (K^+)–channel activity is increased.[2] At higher concentrations, pores are formed in the membrane. Loss of intracellular potassium and other molecules impairs fungal viability. The onset of action is rapid and unrelated to the growth rate, consistent with the concept that the drug acts at preformed sites and no metabolic processing is required before a target is exposed.[3] Alternative explanations of amphotericin B action have been postulated. In one, binding to cell membrane lipids is postulated to have primacy over actions at ion channels.[4] Amphotericin B also has effects via oxidative pathways that may enhance antifungal activity. In addition, amphotericin B localizes to endothelial cells and may thereby produce endothelial cell activation.[5] The possible effects of amphotericin B and its lipid formulations on the immune system have been reviewed.[6]

Spectrum of Activity and Mechanisms of Resistance

Amphotericin B is active against most fungi, and its spectrum of activity is not influenced by the choice of formulation. Where resistance occurs, it is generally attributed to reductions in ergosterol biosynthesis and synthesis of alternative sterols that lessen the ability of amphotericin B to interact with the fungal membrane.[7] Resistance appears modulated by sphingolipids,[8] and may also follow from increased production of reactive-oxidant scavengers.[9] Primary resistance is common for *Aspergillus terreus, Scedosporium* spp., and *Trichosporon* spp.[7] Among the *Candida* spp., primary resistance is noted at meaningful frequencies most often for *Candida lusitaniae* and the newly recognized pathogen, *Candida auris*. Development of resistance in isolates of normally susceptible species is rare but has been described for essentially all common pathogens. Although such isolates may exhibit altered growth and reduced pathogenicity,[10] invasive and lethal infections are well described. Cell wall changes in resistant strains may also have immunologic consequences.[11] In studies of amphotericin B deoxycholate as therapy for candidiasis, the principal pharmacodynamic driver of in vivo response has been ratio of the peak achieved serum concentration to the minimal inhibitory concentration.[12]

AVAILABLE FORMULATIONS

There are four principal available amphotericin B formulations. Amphotericin B deoxycholate (ABD; Fungizone) was licensed in 1959 in the United States.[13] Subsequently, three lipid-associated formulations have been marketed: amphotericin B colloidal dispersion (ABCD; Amphotec or Amphocil), amphotericin B lipid complex (ABLC; Abelcet), and liposomal amphotericin B (LAMB; AmBisome).[14] Other lipid amphotericin preparations, including liposomal preparations, have emerged in markets outside the United States; that they are equivalent in efficacy and toxicity to ones marketed in the United States has not been shown. In attempts to produce lower-cost lipid-associated formulations, some reports have advocated mixing ABD with a parenteral fat emulsion at an ABD concentration of 1 to 2 mg/mL. Although less nephrotoxicity in adults has been suggested with this preparation, at a dose of 1 mg/kg daily, than with infusions of ABD in 5% dextrose,[15] no advantage was found in children,[16] and serum amphotericin B concentrations were also lower with the fat emulsion, thus raising the possibility that amphotericin B was simply aggregating in the fat emulsion, but that the resulting cloudiness could not be perceived in the milky-looking lipid. Use of such preparations should be reserved for investigational settings.

Amphotericin B Deoxycholate Formulation

ABD is insoluble in water at physiologic pH. The drug is marketed for intravenous (IV) use as a powder containing amphotericin B, 50 mg; sodium deoxycholate, 41 mg; and sodium phosphate buffer, 25.2 mg. Although a clear yellow solution forms when the powder is hydrated, ABD is colloidal. If a filter with a 0.22-micropore diameter is placed in the infusion line, considerable drug is removed by the filter. ABD must be prepared by dissolving in water or dextrose in water: dissolution in electrolyte-containing diluents (e.g., sodium chloride or sodium bicarbonate) will aggregate the colloids, producing visible clouding, and must be avoided. ABD is currently manufactured by a number of different generic manufacturers, and significant differences in amphotericin A contamination and the ability of the product to induce interleukin-1β production have been reported and may be part of the cause of the intersubject variation in toxicities observed with such compounds.[17]

Pharmacology

Concentrations of amphotericin B in biologic fluids have usually been measured by bioassay,[18] but use of high-pressure liquid chromatography,[19,20] immunoassay,[21] and radiometric respirometry[22] have been described. Despite the proliferation of methods, routine determination of amphotericin B serum, urine, or cerebrospinal fluid (CSF) concentrations has no definite clinical value. Nonetheless, amphotericin B assays have revealed some remarkable pharmacologic properties of ABD. When colloidal amphotericin B is admixed in serum, deoxycholate separates from amphotericin B, and more than 95% of the latter binds to serum proteins, principally to β-lipoprotein. Presumably the drug is bound to the cholesterol carried on this protein. Most of the drug leaves the circulation promptly, perhaps bound to cholesterol-containing cytoplasmic membranes. Amphotericin B is stored in the liver and other organs; the drug appears to reenter the circulation slowly. Most of the drug is degraded in situ, with only a small percentage being excreted in urine or bile. Blood levels are uninfluenced by hepatic or renal failure. Hemodialysis does not alter blood levels, except in an occasional patient with lipemic plasma, who may be losing drug by adherence to the dialysis membrane. Concentrations of amphotericin B in fluid from inflamed areas, such as pleura, peritoneum, joints, vitreous humor, and aqueous humor, are roughly two-thirds of the trough serum level. Cord blood from one infant contained an amphotericin B concentration of 0.37 μg/mL, half the simultaneous maternal trough blood level. Amphotericin B penetrates poorly into CSF (whether meninges are normal or inflamed), saliva, bronchial secretions, brain, pancreas, muscle, bone, vitreous humor, or normal amniotic fluid. The presence of infection and inflammation in some tissues may increase the local concentrations. Urine concentrations are similar to serum concentrations. Peak serum concentrations with conventional IV doses are 0.5 to 2.0 μg/mL and

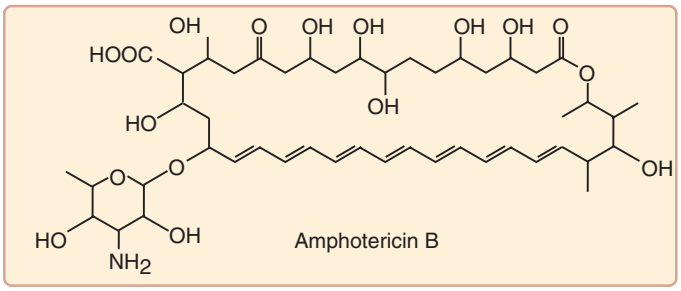

FIG. 40A.1 Structure of amphotericin B.

rapidly fall initially to slowly approach a plateau of 0.2 to 0.5 μg/mL.[18] The initial half-life is about 24 hours; the β-phase half-life is roughly 15 days. Serum concentrations can be detected for at least 7 weeks after the end of therapy, presumably reflecting release from cell membranes and/or lipids. The drug also has complex immunomodulatory properties, potentially of clinical significance but presently undefined.

Toxicity

Nephrotoxicity

ABD causes a dose-dependent decrease in the glomerular filtration rate. The direct vasoconstrictive effect of amphotericin B on afferent renal arterioles results in reduced glomerular and renal tubular blood flow.[23] Other primary or secondary effects on the kidney include potassium, magnesium, and bicarbonate wasting and decreased erythropoietin production. Permanent loss of renal function is roughly related to the total dose, not the level of temporary azotemia, and is due to destruction of renal tubular cells, disruption of tubular basement membrane, and loss of functioning nephron units. Methodologies to detect early signs of kidney damage are under study.[24] Saline loading, such as infusion of 1 L of saline before ABD, has been associated with reduced nephrotoxicity in some studies but not others.[25] Benefits from oral salt loading have also been reported.[26] Serum potassium should be monitored, and losses often require supplemental oral or IV potassium. Renal tubular acidosis from bicarbonate wasting rarely requires base replacement, but other drugs and diseases that promote acidosis may act synergistically.

Amphotericin B is generally devoid of drug-drug interactions, but azotemia caused by amphotericin B is often worse in patients taking other nephrotoxic drugs, such as cyclosporine or aminoglycosides. Hypotension, intravascular volume depletion, renal transplantation, and other preexisting renal disease all magnify the management problems associated with amphotericin B–induced azotemia. These toxicities are lessened by use of the lipid-associated formulations of amphotericin B (LFABs; see "Lipid-Associated Formulations of Amphotericin B" later).

Early in a course of therapy with ABD, azotemia may increase rapidly, often falls a little, and then stabilizes after several days. Adults with no other renal disease may develop an average serum creatinine level of 2 to 3 mg/dL at therapeutic doses, and therapy should not be withheld unless azotemia exceeds this level. Attempting to give ABD to an adult without causing azotemia will usually lead to inadequate therapy. The purpose of tapering therapy is not to avoid drug accumulation, but to reduce insults to already damaged nephrons.

Other Chronic Toxicity

Nausea, anorexia, and vomiting are common. Phlebitis occurs if peripheral vein catheters are used. Normocytic normochromic anemia occurs gradually and is associated with lower plasma erythropoietin levels than anticipated from the level of anemia.[27] The hematocrit rarely falls below 20% to 25% unless other causes of anemia are present. Rarely, thrombocytopenia, modest leukopenia, arrhythmias, coagulopathy, hemorrhagic enteritis, tinnitus, vertigo, encephalopathy, seizures, hemolysis, elevated transaminases, or dysesthesia of the soles of the feet may be observed.

Acute Reactions

About 30 to 45 minutes after beginning the first few ABD infusions, chills, fever, and tachypnea may occur, peak in 15 to 30 minutes, and slowly abate over a period of 2 to 4 hours. A patient with underlying cardiac or pulmonary disease may have hypoxemia. These reactions are less common in young children or patients receiving adrenal corticosteroids. Subsequent infusions of the same dose cause progressively milder reactions. Premedication with acetaminophen or the addition of hydrocortisone, 25 to 50 mg, to the infusion solution can diminish the reactions. Meperidine given early in a chill shortens the rigors but may induce nausea or emesis. Concern about this kind of reaction in an unstable patient had led some physicians to use a test dose of 1 mg given over a 15-minute period to assess the subsequent reaction over 1 hour before deciding whether the next dose should be a full therapeutic dose of at least 0.5 mg/kg or an intermediate dose. Whether or not a test dose is given, patients with rapidly progressive mycoses should receive a full therapeutic dose within 24 hours, without any delay entailed by test or intermediate doses. Equally important, this reaction should not be mistaken for anaphylaxis or otherwise considered a contraindication to further ABD. True allergic reactions are extremely rare. Reversible dilated cardiomyopathy has been reported.[28]

Administration

ABD is infused in 5% dextrose over a 2- to 4-hour infusion interval. Infusion 1 hour in duration appears to generally be safe for persons who have tolerated slower infusions and may be advantageous for outpatient therapy.[29,30] Early in the course of therapy, fever is more pronounced with infusion intervals of only 45 minutes than with infusion lasting 4 hours.[31] Rapid infusion in patients with severely compromised renal function may lead to acute, marked hyperkalemia and ventricular fibrillation. Particularly with infusions of prolonged length, shielding the infusion bottle from light would reduce drug decay from light sensitivity.

Once therapy is well underway, patients receiving a stable daily dose may be changed to an increased double dose on alternate days to reduce the frequency of infusion-associated toxicity, particularly anorexia, and as a convenience for outpatient therapy. Doses greater than 1.5 mg/kg are not generally given on this schedule because the toxicity of such infusions is not well described. As another approach to reduction of toxicity, continuous infusion of amphotericin B with doses up to 2.0 mg/kg per 24 hours has been described based on limited data,[32] but this approach is not consistent with the observation that the principal pharmacodynamic driver of efficacy for amphotericin B is peak drug concentration.[33,34]

Dosage

Daily ABD doses of 0.3 mg/kg often suffice for esophageal candidiasis. A dose of 0.5 mg/kg is appropriate for blastomycosis, disseminated histoplasmosis, and extracutaneous sporotrichosis. Patients with cryptococcal meningitis are generally given doses of 0.6 to 1 mg/kg; those with coccidioidomycosis may require doses of 1 mg/kg. Patients with mucormycosis or invasive aspergillosis are given daily doses of 1 to 1.5 mg/kg until improvement is clearly present. Doses of 0.5 to 1.0 mg/kg are often used in neutropenic patients receiving empirical amphotericin B (see Chapter 306).[35] Local instillation of amphotericin B into CSF, joints, or pleura is rarely indicated. One exception is coccidioidal meningitis, which can be treated with intrathecal amphotericin B because it may produce superior results, particularly in the long term, although with far greater toxicity than seen with systemic azole therapy. Intraocular administration for fungal endophthalmitis is occasionally used; doses of 5 to 10 μg appear to avoid retinal toxicity. Corneal baths with 1 mg/mL in sterile water are useful for fungal keratitis but are irritating. Bladder irrigation with 50 μg/mL in sterile water is useful for patients with *Candida* cystitis and a Foley catheter, particularly as preparation for genitourinary surgery. Equivalent results may be obtained with oral fluconazole.

Lipid-Associated Formulations of Amphotericin B

One of the LFABs (LAMB; trade name AmBisome) is a liposomal formulation. The other two—ABLC (trade name Abelcet) and ABCD (two trade names: Amphotec and Amphocil)—are aggregates of lipid and amphotericin B rather than liposomes. The phrase "liposomal

amphotericin B" is often used mistakenly as a label for the entire class of compounds. Thus this chapter uses the phrase *lipid-associated formulations of amphotericin B* (LFABs) as a general label for the class. Because tolerance of one product does not always translate to tolerance of another, it is important that the physician use an unambiguous name when prescribing these compounds.[36]

ABLC is licensed in the United States for treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy (5 mg/kg/day).[37] LAMB is licensed for empirical therapy for presumed fungal infection in febrile, neutropenic patients (3 mg/kg/day); for treatment of cryptococcal meningitis in human immunodeficiency virus (HIV)–infected patients (6 mg/kg/day); for treatment of patients with *Aspergillus* spp., *Candida* spp., and/or *Cryptococcus* spp. infections refractory to ABD; or in patients in whom renal impairment or unacceptable toxicity precludes the use of ABD. LAMB is also indicated for treatment of visceral leishmaniasis (3 mg/kg/day for immunocompetent patients, 4 mg/kg/day for immunocompromised patients; see Chapter 275 for further details).[38] ABCD is not presently commercially available in the United States.

Pharmacology and Toxicity

The three LFABs have quite different pharmacokinetic patterns.[12,13] When compared on the basis of equal milligram-per-kilogram dosages, the LFABs produce tissue amphotericin B concentrations that range from 10% to 500% of those seen with ABD,[12] with a consistent relative reduction (80%–90%) seen in the kidney concentration. Because the LFABs are typically given at milligram-per-kilogram doses that are 3- to 12-fold higher than those used for ABD, the relevance of these comparisons is uncertain, although it is generally clear that all three LFABs require higher doses in experimental animals to achieve the same therapeutic effect as ABD.

These higher but equipotent doses of the LFABs are notably better tolerated than ABD, with reductions in both the frequency and severity of acute infusion-related reactions and chronic nephrotoxicity.[39] An exception to this rule is ABCD, which generally shows acute infusion-related reactions similar to or worse than those with ABD.

Intolerance to one LFAB but not to another has been rarely reported, and allergy to some component of the offending preparation has been speculated.

Amphotericin B Lipid Complex

ABLC is a complex of almost equimolar concentrations of amphotericin B and lipid, the latter being a 7:3 mixture of dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol. The drug is shipped as a cloudy suspension with particles 1.6 to 11 μm in diameter. Particle shape is not globular but ribbon-like. The manufacturer provides a device for the pharmacy to filter out aggregates larger than 5 μm before dispensing in 5% dextrose solution. The major efficacy data are from the manufacturer's open-label, noncomparative studies.[40,41]

Liposomal Amphotericin B

LAMB comprises a unilamellar liposome about 55 to 75 nm in diameter that contains roughly one molecule of amphotericin B per nine molecules of lipid. The latter is a mixture of hydrogenated soy lecithin–cholesterol-distearoylphosphatidylglycerol in a 10:5:4 ratio. Unlike the other lipid-associated amphotericins, serum concentrations are not lower than those obtained with the same dose of ABD, the circulating drug is liposome-associated after IV infusion, and the amount of unbound amphotericin is less than with ABD.[42] In a randomized three-way trial comparing LAMB at 3 or 6 mg/kg/day and ABD at 0.7 mg/kg/day in HIV-infected subjects with cryptococcal meningitis, equivalent global response rates were reported. A randomized comparison of LAMB versus ABD for histoplasmosis in HIV-infected subjects reported superior efficacy for LAMB.[43] Prospective randomized studies have compared LAMB and ABD in neutropenic patients with fever and found equivalent efficacy.[44,45] Randomized trials in patients with aspergillosis indicated doses of 1 to 3 mg/kg LAMB to be not inferior in efficacy to doses of 4 to 10 mg/kg, and with fewer side effects.[46,47]

These studies generally suggest that LAMB causes less nephrotoxicity and less severe hypokalemia than ABD, a result supported by a direct comparison of the two formulations, and less nephrotoxicity than ABLC.[48,49] Infusion at 1 to 2 mg/mL over a 2-hour period is recommended. Infusion intervals can be shortened to 60 minutes for patients in whom the treatment is well tolerated. A triad of infusion-related reactions—symptoms from the categories of (1) chest pain, dyspnea, and hypoxia; (2) severe pain in the abdomen, back, flank, or leg; and (3) flushing and urticaria—have been reported to occur, most often within the first 5 minutes of infusion and apparently unrelated to infusion speed.[50] These reactions are effectively managed by administration of diphenhydramine and brief interruption of the LAMB infusion. LAMB is the only LFAB that does not contraindicate the use of an in-line filter, although pore size should be at least 1.0 μm. Pseudohyperphosphatemia has been reported in children.[51]

Comparison of Amphotericin B Deoxycholate and the Lipid-Associated Formulations of Amphotericin B

Randomized clinical trials comparing ABD as therapy for a defined mycosis are limited to the demonstrations for LAMB of similar efficacy for cryptococcal meningitis and greater efficacy for histoplasmosis.[43] Randomized comparisons with ABD as therapy in the persistently neutropenic and febrile cancer patient provide consistent demonstrations of a generally better tolerability profile, but there are few data on differential antifungal effect. Consistent with these results, the aggregate open-label data efficacy rates for the LFABs are similar to those for ABD.[13] Although the LFABs are notably more costly (10- to 60-fold) than ABD, the purchase cost of the compound must be balanced against the morbidity and financial costs of monitoring, treating, and managing ABD-related nephrotoxicity. Of importance, such toxicity may be well tolerated in an outpatient with few other comorbidities or in children, whereas ABD-related nephrotoxicity (50% increase in baseline creatinine to a minimum of 2 mg/dL) was associated with a 6.6-fold increased odds of death and an absolute increase in mortality from 16% to 54%.[52] In the majority of patients, LAMB or ABLC is preferred over ABD.

The lipid-associated amphotericins also remain valuable agents when compared with the azoles and echinocandins. Although associated with more adverse events than agents from these two other classes, ABLC and LAMB remain appropriate for acute management of severe disseminated histoplasmosis, initial management of cryptococcosis, and treatment of suspected mucormycosis. They also provide important options for management of the persistently febrile neutropenic patient (particularly when this syndrome develops despite prophylaxis with an azole that has activity against molds) and for treatment of selected cases of candidiasis.[53] The advantage of prolonged blood levels has caused some centers to explore infusions given one to three times per week for prophylaxis in leukopenic or immunosuppressed patients.

Other Routes for Amphotericin B

Inhalation of amphotericin B has been used both therapeutically and prophylactically, but the supporting data for this practice are relatively sparse.[54] Nebulized forms of the lipid-associated amphotericins have been better tolerated than ABD, in part because of the bitter taste of the bile salt. Formal studies on prophylaxis in high-risk populations have shown encouraging results.[55] An argument has been made that the aerosol might decrease *Aspergillus* infections in lung transplant recipients, including infections at the bronchotracheal anastomotic site.[56–58]

Many researchers have tried to develop formulations of amphotericin B that could be given by the oral route, and studies of nanoparticles or microemulsions are promising in avoiding gastric degradation and promoting intestinal uptake.[59,60]

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40B Antifungal Drugs: Azoles

George R. Thompson III

SHORT VIEW SUMMARY

- Azole antifungals differ from nitroimidazole drugs such as metronidazole in that azole antifungals have no clinical activity against bacteria. Azoles include triazoles, with three nitrogens, and imidazoles, with two nitrogens.
- Azoles inhibit synthesis of ergosterol by blocking lanosterol 14α-demethylase. Azole resistance arises from mutations in the gene (*ERG11* or *CYP51*) coding for the demethylase or by increased drug efflux from the fungal cell.
- A wide variety of imidazoles are available for topical treatment of dermatophyte infections and vulvovaginal candidiasis.
- Triazoles such as fluconazole have replaced imidazoles such as ketoconazole for the treatment of systemic mycoses due to improved oral absorption and more favorable side-effect profiles.
- The systemically active triazoles have overlapping antifungal spectra, with some exceptions.
  - Fluconazole is not active against molds but is used in the treatment of invasive candidiasis, cryptococcosis, and coccidioidomycosis.
  - Voriconazole has proven efficacy in invasive aspergillosis and candidiasis, plus some reports of activity in endemic mycoses and hyaline molds, but is notably not useful in mucormycosis.
  - Posaconazole is effective as prophylaxis in certain immunosuppressed populations and in the treatment of some cases of mucormycosis.
  - Isavuconazole is noninferior to voriconazole in the treatment of invasive aspergillosis and is active against some agents of mucormycosis.
  - Itraconazole remains the azole of choice for blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis.
- All triazoles have drug-drug interactions (Table 40B.2) primarily through cytochrome P-450 3A4, with itraconazole having the most and fluconazole (and possibly isavuconazole) having the least.
- Of the currently available triazoles, only fluconazole has significant concentrations in urine.
- Fluconazole has the most predictable serum concentrations, and itraconazole and voriconazole have the least predictable serum concentrations, with posaconazole and isavuconazole in between.

The azole antifungal agents contain either two or three nitrogens in the azole ring and are classified as imidazoles (ketoconazole, miconazole, econazole, and clotrimazole) or triazoles (fluconazole, itraconazole, posaconazole, voriconazole, and isavuconazole), respectively (Fig. 40B.1). The imidazoles were previously used for systemic therapy but have been relegated to topical agents in the treatment of dermatophytosis and cutaneous or mucosal *Candida* infections.

The triazoles exert their effects within ergosterol synthesis by complexing the heme group of the cytochrome P-450 (CYP)–dependent lanosterol 14α-demethylase, preventing the conversion of lanosterol to ergosterol.[1] This inhibition leads to an increase in methyl sterols, causing a disruption of the packed acyl chains of fungal phospholipid cell membranes, and reduces the concentration of ergosterol—a sterol essential for normal fungal cytoplasmic membrane function. Following this destabilization of membrane-associated enzymes and the normal membrane structure and function, fungal growth is inhibited.

Techniques for in vitro susceptibility are available as standardized methodologies.[2,3] Reference documents have been composed providing detailed instructions for in vitro susceptibility testing of the most frequently encountered yeasts and molds, and standardization of these processes has facilitated attempts to establish clinically predictive breakpoints for susceptibility testing. This remains a work in progress and a source of ongoing controversy.

The principal pharmacokinetic predictor of triazole efficacy has been the ratio of total drug exposure (area under the curve) to the mean inhibitory concentration. This ratio has been found predictive of in vivo efficacy in studies of *Candida, Cryptococcus,* and *Aspergillus* spp.[4–6] Doses are outlined in Table 40B.1.

The triazoles exhibit significant differences in their affinity for the lanosterol 14α-demethylase enzyme, and these differences are largely responsible for their varying antifungal potency and spectrum of activity. Cross-inhibition of several human CYP-dependent enzymes (CYP3A4, CYP2C9, and CYP2C19) is responsible for most of the clinical side effects and drug-drug interactions within this class.[7] These interactions differ substantially between agents, and key interactions are summarized in Table 40B.2.

MECHANISMS OF TRIAZOLE RESISTANCE

The availability of the triazoles has been a welcome advance in the treatment of invasive fungal infections; however, resistance to these agents represents a significant and ongoing challenge. Resistance to triazoles occurs primarily through increased lanosterol 14α-demethylase expression, alterations in the binding site, or drug efflux.[8] Resistant species, whether inherently resistant or with acquired resistance, complicate management, and invasive fungal infections may break through or develop during antifungal therapy.

Candida albicans remains the most common *Candida* species, and although resistance to fluconazole and other triazoles has been described, it remains relatively uncommon in cases of candidemia (0%–5%).[9] Patients with oropharyngeal candidiasis, particularly recurrent disease, have been found to harbor triazole-resistant *C. albicans,* and overexpression of genes encoding lanosterol 14α-demethylase (*ERG11*) and efflux transporters (*MDR1*, *CDR1*, *CDR2*) have been found to be responsible in most cases, with amino acid substitutions less frequently observed.[10] In some centers, *Candida glabrata* is the second most common cause of invasive candidiasis, and this species exhibits frequent resistance to azoles mediated by changes in drug efflux (Cdr1 and Cdr2).[11] This can often be overcome by higher triazole dosing; however, for invasive infections an alternative antifungal class is recommended.[12] The ability of *C. glabrata* to develop resistance to multiple drug classes including triazoles and echinocandins has been associated with a mutator phenotype caused by a mismatch repair defect prevalent in *C. glabrata* clinical isolates.[13] Fluconazole resistance in *C. glabrata* is largely due to drug efflux. *Candida krusei* is inherently resistant to fluconazole due to changes within *ERG11,* although it typically remains susceptible to alternative triazole agents.[14] Resistance to triazoles among other common *Candida* spp. (e.g., *C. parapsilosis, C. guillermondii, C. tropicalis*) is infrequent.

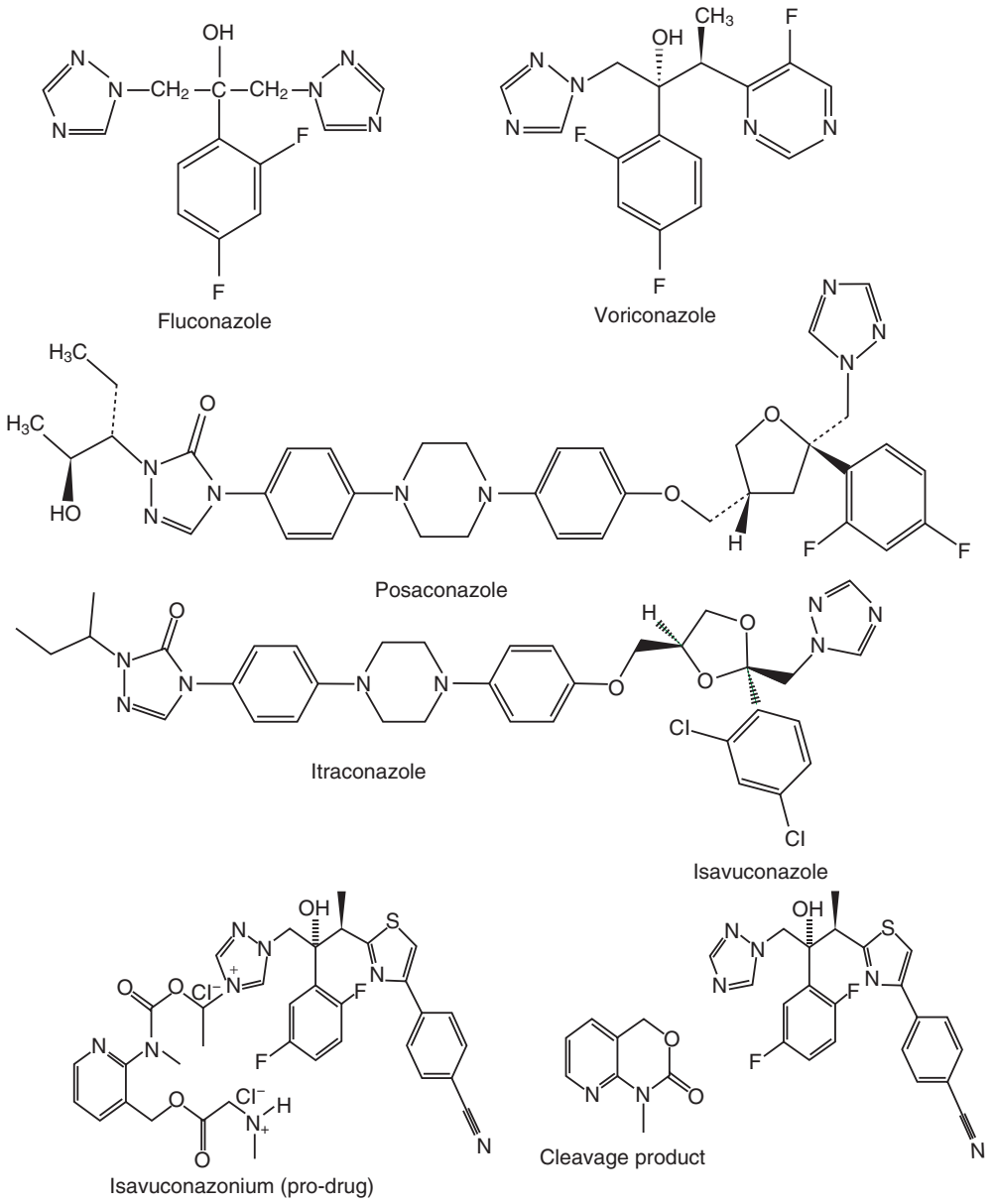

FIG. 40B.1 **Structures of clinically available triazoles used for systemic antifungal therapy.**

TABLE 40B.1 Dosing of Triazoles in Treatment of Systemic Fungal Infection

AZOLE	ADULT DOSE	FREQUENCY	ROUTE	LOADING	NOTE
Fluconazole	400 mg	Daily	PO, IV	None	
Itraconazole	200 mg	Daily or twice daily	PO	None	Suspension or capsule
Conventional formulation: suspension or capsules	200 mg	Daily or twice daily	PO	None	
Enhanced bioavailability SUBA-itraconazole formulation	65 mg	Daily or twice daily	PO	130 mg 3 times daily for first 3 days in life-threatening situations	
Posaconazole					
Suspension	200 mg	Three or four times daily	PO	None	
Tablets	300 mg	Once daily	PO, IV	300 mg q12h on day 1	
Voriconazole	4 mg/kg	Twice daily	PO, IV	6 mg/kg q12h on day 1	
Isavuconazole	200 mg	Once daily	PO, IV	200 mg q8h for 6 doses	

[a]Alternative dosing strategies may be needed in select clinical circumstances.

The emergence of *Candida auris* and subsequent nosocomial outbreaks has been of particular concern, as the large majority of isolates are resistant to fluconazole (due to *ERG11* mutations) with variable susceptibility to other azoles, and amphotericin B and echinocandin resistance rates are approximately 30% to 40% and up to 5% to 10%, respectively.[15] *Candida* isolates developing cross-resistance between triazoles and amphotericin B have been found to harbor mutations within other steps of the ergosterol biosynthetic pathway (*ERG2* and *ERG3*)[16,17] or the acquisition of simultaneous mutations in several genes, resulting in the development of multidrug resistance.[18,19]

TABLE 40B.2 Synopsis of Azole Drug-Drug Interactions

DRUG	FLUCONAZOLE	VORICONAZOLE	ITRACONAZOLE[a]	POSACONAZOLE	ISAVUCONAZOLE
Azole Causes Increased Blood Levels of Other Drug					
Alfentanil		Yes	Yes		
Alprazolam		Yes	Yes		
Astemizole	Yes	Yes[b]	Yes	Yes	
Bortezomib			Yes		
Budesonide	Yes	Yes	Yes	Yes	Yes
Calcium channel blockers		Yes	Yes	Yes	
Carbamazepine	Yes		Yes		
Cisapride	Yes[b]	Yes[b]	Yes	Yes	
Coumarin-type anticoagulants including warfarin	Yes	Yes	Yes		
Cobicistat			Yes		
Cyclosporine	Yes	Yes	Yes	Yes	Yes
Digoxin		No	Yes	Yes	Yes
Disopyramide			Yes		
Dofetilide			Yes		
Ergot alkaloids		Yes[b]	Yes	Yes	
HMG-CoA reductase inhibitors ("statins")		Yes	Yes	Yes	Yes
Ibrutinib	Yes	Yes	Yes	Yes	Yes
Levacetylmethadol (levomethadyl)			Yes		
Methadone	Yes	Yes	Yes		
Midazolam (and other short-acting benzodiazepines)	Yes	Yes[b]	Yes	Yes	Yes
Mycophenolate					Yes
Nevirapine			Yes		
Nisoldipine			Yes		
Nortriptyline			Yes		
Omeprazole		Yes			
Oral hypoglycemics (e.g., glyburide, glipizide)	Yes	Yes	Yes	No for glipizide	
Phenytoin	Yes	Yes	Yes	Yes	
Pimozide	Yes	Yes[b]	Yes	Yes	
Prednisolone		Yes			
Quinidine	Yes	Yes[b]	Yes	Yes	
Rifabutin	Yes	Yes[b]	Yes	Yes	
Rivaroxaban	Yes				
Ruxolitinib	Yes	Yes	Yes	Yes	Yes
Saquinavir, ritonavir, and other protease inhibitors	Yes	Yes	Yes	Yes	
Sirolimus	Yes	Yes[b]	Yes	Yes	Yes
Tacrolimus	Yes	Yes	Yes	Yes	Yes
Terfenadine	Yes[b]	Yes[b]	Yes	Yes	
Theophylline	Yes[c]				
Tofacitinib	Yes	Yes	Yes	Yes	Yes
Triazolam	Yes	Yes	Yes	Yes	
Vinca alkaloids (vincristine, vinblastine)		Yes	Yes	Yes	
Azole Level Is Reduced by Other Drug					
Antacids of any type (H2 blocker or PPI)	No	No	Yes	Yes for suspension[d], no for tablets	
Carbamazepine	Yes	Yes[b]	Yes	Yes	Yes[b]
Efavirenz		Yes[c]	Yes	Yes	

Continued

TABLE 40B.2 Synopsis of Azole Drug-Drug Interactions—cont'd

DRUG	FLUCONAZOLE	VORICONAZOLE	ITRACONAZOLE[a]	POSACONAZOLE	ISAVUCONAZOLE
Fosamprenavir				Yes	
Isoniazid			Yes		
Long-acting barbiturates		Yes[b]			Yes[b]
Metoclopramide				Yes for suspension, no for tablets	
Nevirapine		Yes	Yes		
Phenobarbital		Yes[b]	Yes		
Phenytoin		Yes	Yes	Yes	
Rifabutin		Yes[b]	Yes	Yes	
Rifampin	Yes	Yes[b]	Yes	Yes	Yes[b]
Ritonavir		Yes[b]			
St. John's wort		Yes[b]	Yes		Yes[b]

[a]In addition, itraconazole levels are increased by clarithromycin, erythromycin, indinavir, and ritonavir.
[b]Absolute contraindication.
[c]Concurrent usage requires unusually careful dose adjustments and monitoring.
[d]When given concomitantly with the suspension formulation, cimetidine and esomeprazole have been shown to reduce plasma posaconazole levels.
HMG-CoA, 3-Hydroxy-3-methylglutaryl coenzyme A; *PPI,* proton pump inhibitor.
Note: Azoles are involved in drug-drug interactions either by interfering with metabolism and thus increasing the concentration of other drugs or by having their level reduced via either induction of hepatic metabolism or reduced absorption. The principal interactions are via CYP3A4 (all azoles) plus CYP2C9 (fluconazole, voriconazole) and CYP2C19 (fluconazole, voriconazole). Because of the differential distribution of the cytochrome P-450 enzymes in the liver and gut, the magnitude of drug-drug interactions may be influenced by the route of drug administration. For example, the effect of voriconazole on tacrolimus is even more pronounced (higher tacrolimus levels) when voriconazole is given orally rather than intravenously. Key interactions found in the US prescribing literature are listed above; for more exhaustive reviews, drug-interaction software (e.g., Lexicomp) are also available. Blanks in this table signify absence of data and not absence of interaction.

Triazole resistance has similarly been described in *Cryptococcus* spp., with recurrence of disease during fluconazole maintenance therapy increasingly reported.[20] In a recent review, up to 12% of all cryptococcal isolates were found to have decreased fluconazole susceptibility.[21] In contrast to *Candida* spp., most azole-resistant cryptococcal strains exhibit unstable resistance, described as heteroresistance. Resistance in these isolates represents a transient adaptation to drug pressure, and detailed investigation has found resistance is not due to mutations within *ERG11* or efflux genes, but rather is due to duplications of chromosome 1 (harbors *ERG11* and the efflux pump *AFR1*).[22] This phenomenon is readily observed in vitro for *Cryptococcus* spp.; however, the importance of in vivo resistance by this mechanism is less clear.

The emergence of less common but clinically important non-*Candida*, non-*Cryptococcus* yeasts including *Trichosporon, Saprochaete, Magnusiomyces, Saccharomyces, Wickerhamomyces (Pichia),* and *Rhodotorula* has complicated the treatment and prophylaxis of the expanding immunocompromised population.[23] Although most of these species exhibit in vitro susceptibility to fluconazole, *Rhodotorula* spp. are uniformly resistant,[24] and breakthrough infections despite fluconazole therapy have been described in *Saprochaete* and *Wickerhamomyces (Pichia)* infections.[23]

Triazole resistance in *Aspergillus* has been increasingly described and may occur de novo or after treatment. Epidemiologic surveys have been undertaken to understand the burden of resistant *Aspergillus,* with resistance rates differing substantially between regions.[25] Acquired resistance in *Aspergillus fumigatus* is frequently caused by point mutations in CYP51A, the lanosterol 14α-demethylase enzyme in *Aspergillus* spp. Different mutations cause differential triazole susceptibility, with some causing resistance to voriconazole and isavuconazole, and others causing resistance to posaconazole and itraconazole, whereas others are responsible for pan-azole resistance.[26] De novo resistance has been attributed to the use of agricultural triazole fungicides[27] due to the presence of a 34- or 46-base pair tandem repeat in the promoter coupled with a point mutation in the *cyp51A* target gene. This leads to an amino-acid substitution at codon 98 (TR34/L98H) causing multi-azole resistance, or TR46/Y121F/T289A causing reduced voriconazole susceptibility and attenuation of itraconazole and posaconazole activity.[26,28] Other mutations and non-*cyp51A*–mediated mechanisms have also been described.[29,30] Other species such as *Aspergillus tubingensis* and *Aspergillus calidoustus* may be resistant to triazoles, so susceptibility testing of those cryptic species is typically recommended.[31]

The agents of mucormycosis are inherently voriconazole resistant, and more recent work has identified a characteristic *CYP51* sequence in *Mucorales* spp. responsible for this phenotype.[32] *Scedosporium* and *Fusarium* spp. are also frequently resistant to triazoles, whereas *Lomentospora* (formerly *Scedosporium*) *prolificans* is almost uniformly resistant to all clinically available agents.

FLUCONAZOLE (DIFLUCAN)

Formulations and Pharmacology

Fluconazole is available in 50-, 100-, 150-, and 200-mg tablets; a powder for oral suspension; and an intravenous (IV) formulation of either 200 or 400 mg, both as 2 mg/mL. Fluconazole is an attractive agent because of its low cost, relatively dose-dependent adverse-effect profile, tolerability, and excellent oral bioavailability. Following oral ingestion, most drug can be found in the circulation (>90%), and 80% of drug appears unchanged in the urine. Oral absorption is unaltered by food or gastric pH.[33]

Fluconazole exhibits cerebrospinal fluid (CSF) concentrations approximately 50% to 70% of CSF concentrations found in the serum and penetrates the brain.[34] Fluconazole is widely distributed in body fluids, and excellent concentrations have been found in the saliva, sputum, urine, and other body fluids and tissues and is not significantly protein bound (approximately 10%).[35,36]

The relatively long half-life (approximately 30 hours) allows for once-daily dosing of fluconazole (see Table 40B.1). In patients with a creatinine clearance <50 mL/min a dose reduction of 50% is required, and patients with a creatinine clearance <20 mL/min require a reduction to 25% of the normal dose. A loading dose of twice the daily dose is recommended. Patients receiving dialysis should receive 100% of the normal daily dose after each dialysis session and on nondialysis days a reduced dose according to their creatinine clearance. Preterm infants (body weight <1000 g) prescribed fluconazole prophylaxis are prescribed 3 to 6 mg/kg twice weekly for 6 weeks.

Drug Interactions

Fluconazole is a strong inhibitor of CYP2C19 and CYP2C9 and a moderate inhibitor of CYP3A4, and significant drug-drug interactions can thus occur. Concurrent therapy with medications metabolized

through CYP3A4 with the potential to prolong the QT interval (e.g., cisapride, astemizole, pimozide, and quinidine) is contraindicated.

Side Effects

Adverse effects from fluconazole are generally benign; however, both hepatotoxicity and cardiac toxicity due to prolongation of the QTc interval can occur with any of the triazoles, and neither hepatotoxicity nor cardiac toxicity is clearly dose or time dependent. Headache, alopecia, xerosis, and cheilitis are the most frequent side effects of fluconazole and are reversible after discontinuation of therapy.[37] Neurotoxicity has been reported with very high doses (2000 mg daily) before the availability of alternative triazoles.[38] Anaphylaxis and Stevens-Johnson syndrome have been rarely observed. Fluconazole is a known teratogen and is listed by the US Food and Drug Administration (FDA) as a category D agent. An analysis found no association of fluconazole with birth defects noted in prior reports, although exposure may confer an increased risk of tetralogy of Fallot.[39]

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) of fluconazole therapy is not generally recommended due to its high bioavailability and a lack of defined target serum concentrations.[6] However, at high doses such as those frequently used in coccidioidomycosis[40] or in patients with renal dysfunction or morbid obesity, fluconazole exposure may be profoundly altered and difficult to predict. Monitoring fluconazole serum drug levels may theoretically be useful in these settings.

Indications

Candidiasis

Fluconazole (100–200 mg daily) is one of most effective agents for oropharyngeal candidiasis. Daily therapy (200–400 mg) for 14 to 21 days is also effective in the management of esophageal candidiasis. A single 150-mg tablet is highly efficacious in the treatment of vulvovaginal candidiasis.[12] Symptomatic *Candida* cystitis responds to fluconazole 200 mg daily for 2 weeks. High-risk groups (neutropenic patients, low-birth-weight infants, and patients undergoing urologic procedures) with asymptomatic candiduria similarly respond to fluconazole therapy.[12,41] Although echinocandins are recommend first-line treatment agents in cases of candidemia, fluconazole is an acceptable alternative in selected patients who are not critically ill and are unlikely to have a fluconazole-resistant *Candida* spp. Transition from an echinocandin to fluconazole (step-down therapy) is recommended for patients following clinical improvement and clearance of fungemia.[12] After initial therapy and clearance of blood cultures in candidal endocarditis, fluconazole is often used to prevent relapse.[12]

Cryptococcosis

Preferred induction therapy for acquired immunodeficiency syndrome (AIDS)–associated cryptococcal meningitis includes a lipid formulation of amphotericin B plus flucytosine. Following an appropriate response, consolidation therapy with fluconazole 400 to 800 mg daily should be administered for a minimum of 8 weeks. At the completion of consolidation, maintenance therapy with fluconazole 200 to 400 mg daily for 1 year after diagnosis is frequently recommended and continued until the $CD4^+$ count increases above 100 cells/mm^3 with an undetectable human immunodeficiency virus (HIV) viral load for >3 months.[42] Secondary prophylaxis should be reinitiated if the $CD4^+$ count later decreases again below 100 cells/mm^3. In settings where flucytosine is not available as a component of induction therapy for HIV-positive patients, amphotericin B with fluconazole (800 mg daily) is recommended for 2 weeks followed by fluconazole alone. If no amphotericin B formulations are available, fluconazole 800 to 1200 mg daily plus flucytosine × 2 weeks and fluconazole 800 to 1200 mg daily × 6 weeks are alternative regimens.[43] Treatment of patients with mild-to-moderate pulmonary cryptococcosis for 6 to 12 months with fluconazole 400 mg daily is also recommended.[43]

Other Mycoses

Fluconazole is useful for different manifestations of coccidioidomycosis, including meningitis.[40] Other endemic mycoses have been treated with fluconazole with variable success. In the treatment of histoplasmosis, fluconazole led to improvement in only 54% of cases.[45] Fluconazole treatment of blastomycosis and sporotrichosis has been similarly disappointing.[46,47] Cutaneous dermatophyte infections frequently respond to fluconazole, although other agents are preferred.[48] Fluconazole has no activity against invasive mold infections and should not be used in aspergillosis, mucormycosis, scedosporiosis, and others.

Prophylaxis in Neutropenic Patients

Past reports have evaluated fluconazole in the prevention of fungal infections in bone marrow transplant recipients. These reports illustrate the protective effects of fluconazole against deep-seated candidiasis, although not against aspergillosis.[49,50] Since this time, mold active triazoles have been developed, and multiple trials have been conducted, including two studies demonstrating the superiority of posaconazole compared with fluconazole prophylaxis in high-risk patient populations.[51,52] Other trials have directly compared fluconazole with voriconazole for fungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients, and in this study, fungal-free survival and overall survival did not differ between groups.[53] However, a more recent meta-analysis has suggested that mold-active prophylaxis compared with fluconazole significantly reduces proven and probable invasive fungal infections and fungal-related mortality.[54]

Prophylaxis in Acquired Immunodeficiency Syndrome

Fluconazole, 200 or 400 mg once per week, has reduced the incidence of oral and vulvovaginal candidiasis in patients with advanced HIV infection, but the regimen has not been demonstrated to prevent histoplasmosis, cryptococcosis, or esophageal candidiasis in this population.[55,56] Prophylaxis with 200 mg daily reduces the incidence of oropharyngeal and esophageal candidiasis, as well as cryptococcosis in patients with a $CD4^+$ count of less than 200 cells/mm^3. Cost, lack of effect on survival, and the possibility of azole resistance have led the US Public Health Service/Infectious Diseases Society of America advisory committee to recommend against fluconazole prophylaxis in patients with AIDS. Fluconazole is an alternative to itraconazole for maintenance therapy in patients with AIDS with prior disseminated histoplasmosis.[57]

Prophylaxis in Preterm Neonates

Fluconazole at 3 to 6 mg/kg (every third day for first 2 weeks of life, then every day) until day 30 of life (neonates weighing 1000–1500 g at birth) or day 45 (neonates weighing <1000 g at birth) reduced the rate of invasive *Candida* infection from 13% (placebo) to 2.7% (6-mg group) and 3.8% (3-mg group) in a randomized trial.[58] When evaluated in conjunction with other studies,[59] these data support the use of fluconazole prophylaxis and standard infection control measures for very-low-birth-weight neonates within neonatal care units.

ITRACONAZOLE (SPORANOX) AND ENHANCED BIOAVAILABILITY SUBA-ITRACONAZOLE (TOLSURA/LOZANOC)

Formulations and Pharmacology

Conventional itraconazole is available as a 100-mg capsule, as an oral solution (10 mg/mL) in cyclodextrin as a solubilizing agent, or as an enhanced bioavailability (SUBA-itraconazole) formulation (65-mg capsule). The solution allows for dosing in critically ill patients via the orogastric route or in neonates and children. Oral absorption and daily dosing differs between each formulation. The conventional itraconazole capsule has a bioavailability of approximately 55%, and absorption is improved when given with food and an acidic gastric pH for solubilization. The suspension has 30% to 37% greater bioavailability than that of the capsule, and absorption is not altered by gastric pH, although administration on an empty stomach is optimal for absorption.[60] SUBA-itraconazole should be taken with food, and absorption is enhanced with omeprazole and other acid neutralizing medications. Peak levels are achieved 2 to 6 hours after dosing. Steady state is reached in approximately 14 days, after which time the half-life is 30 to 40 hours. Itraconazole is highly protein bound (99.8%) and undergoes extensive

hepatic metabolism with more than 30 metabolites. One of these, hydroxyitraconazole, has in vitro antifungal activity as well. Itraconazole exhibits poor CSF penetration; however, in both animal and clinical studies, it has proven efficacious in the treatment of fungal meningitis.[61] Renal excretion of itraconazole and hydroxyitraconazole account for less than 1% of the total dose. No dose adjustments have been suggested for use in renal or hepatic impairment, although it should be used with caution in these circumstances.

Drug Interactions

Itraconazole, a strong inhibitor of CYP3A4 as well as P-glycoprotein, is also a substrate for CYP3A4. Significant drug-drug interactions may occur with coadministration of other agents that are metabolized by CYP3A4 or that use P-glycoprotein transporters.[62] In addition, drugs that induce CYP3A4 isozymes may lead to profound increases in itraconazole clearance and subtherapeutic plasma concentrations.[63]

Side Effects

Adverse effects from itraconazole may occur, including hepatotoxicity and QTc prolongation. Gastrointestinal distress is common with the oral suspension. More severe side effects include development of hypertension, hypokalemia, and peripheral edema.[64] This effect was recently determined to be caused by inhibition of human 11β-hydroxysteroid dehydrogenase, causing the syndrome of apparent mineralocorticoid excess.[65] Heart failure has also been described secondary to the negative inotropic effects of itraconazole,[66] and it should be used with caution in patients with a history of ventricular dysfunction of congestive heart failure.[67]

Therapeutic Drug Monitoring

Monitoring of itraconazole serum drug levels is generally recommended due to the erratic absorption and limited bioavailability of current formulations.[6] Target serum levels for itraconazole are generally >0.5 mg/L; however, a concentration effect has been shown in the treatment of most mycoses.[6] Toxicity has similarly been correlated with serum drug levels.[68] It is important to consider the technique used for itraconazole TDM, as bioassay results are typically 2- to 10-fold higher than results obtained by high-performance liquid chromatography (HPLC). HPLC procedures used for TDM quantify both itraconazole and hydroxyitraconazole separately.[69] To make the HPLC assay more reflective of bioassay results, it is common practice to add the concentrations of itraconazole and hydroxyitraconazole together and report a total drug concentration. However, hydroxyitraconazole has more potent activity against the bioassay test organism than itraconazole, a finding that is not necessarily true in patient samples.[70]

Clinical Use

Itraconazole has activity against most cutaneous and invasive mycoses. Allergic bronchopulmonary aspergillosis[71] and invasive aspergillosis[72] both have demonstrated a favorable response to itraconazole therapy. Itraconazole is also useful in the treatment of meningeal[61] and non-meningeal coccidioidomycosis,[73] histoplasmosis,[74] sporotrichosis,[75] blastomycosis,[74] paracoccidioidomycosis,[76] talaromycosis,[77] and the phaeohyphomycoses.[78] Itraconazole is second-line therapy in the treatment of onychomycosis[79] and numerous dermatophyte infections.[80] Chromoblastomycosis has also exhibited a favorable response rate to itraconazole.[81] Itraconazole has been traditionally used for prophylaxis in high-risk neutropenic patients; however, other agents are preferred in this setting following a randomized trial comparing itraconazole or fluconazole prophylaxis with posaconazole solution.[51] Efficacy has also been demonstrated in oral or esophageal candidiasis; however, other agents are preferred, and itraconazole should be reserved for patients intolerant or refractory to other antifungals.[12]

VORICONAZOLE (VFEND)

Formulations and Pharmacology

Voriconazole is available in 50- and 200-mg tablets, a powder for oral suspension, and an IV formulation. Compounded formulations are also available for the treatment of fungal keratitis. Voriconazole has moderate lipophilicity and excellent oral bioavailability (>90%), although absorption is decreased with food by approximately 30%, and administration on an empty stomach is preferred.[7] Voriconazole is widely distributed throughout the body and is able to penetrate the CSF and has demonstrated efficacy in fungal meningitis including the 2012 *Exserohilum* outbreak.[82–84] Voriconazole exhibits nonlinear pharmacokinetics, and the half-life is variable and patient dependent and not useful in predicting the accumulation or elimination of drug. Voriconazole is cleared by hepatic metabolism, and less than 2% of the dose is excreted unchanged in the urine. Dose reduction is required in patients with mild-to-moderate hepatic impairment (Child-Pugh class A or B) with a reduction in the maintenance dosage by 50%. No specific dosage adjustments are indicated with renal impairment. However, the IV form contains a sulfobutyl-β-cyclodextrin for solubility, which is known to accumulate in patients with renal dysfunction, although the clinical implications of this are unclear,[85] and the IV preparation has been safely used in renal dysfunction.[86]

Drug Interactions

Voriconazole undergoes extensive hepatic metabolism and is an inhibitor and substrate of CYP2C19, CYP2C9, and CYP3A4. Significant drug interactions, including bidirectional drug interactions, may occur, and caution with concurrent medications metabolized through these isoenzymes is encouraged.

Side Effects

Adverse effects from voriconazole include hepatotoxicity and QTc prolongation. In addition, there are several unique side effects of voriconazole compared with other triazoles in clinical use. Visual disturbances, including photopsia (the perception of flashing lights), photophobia, and color changes, have been observed and are thought to be secondary to selective and reversible dysfunction of retinal ON-bipolar cells.[87] These effects are usually associated with peak serum concentrations and occur 30 to 60 minutes after oral or IV administration.[88] These effects are reversible and typically resolve over 30 to 60 minutes. No irreversible ocular toxicity has been described. Visual and auditory hallucinations have also been reported and are distinct from photopsia. This effect is usually seen after the first few IV doses of 6 mg/kg and may be more common with elevated serum voriconazole concentrations >5.5 μg/mL.[89] Neurologic toxicity, including confusion, agitation, and myoclonus, are rare and are possibly associated with serum levels exceeding 5.5 μg/mL.

Cutaneous adverse events including rashes and photosensitivity reactions have been seen in approximately 7% of patients.[88] These effects may lead to skin carcinoma following long-term therapy.[90] Although this was initially presumed to be due to a disruption in normal retinol metabolism by voriconazole, this has not been demonstrated.[91] Alopecia, xerosis, and nail changes can also be seen with long-term voriconazole use.[92]

Voriconazole is the only trifluorinated antifungal in clinical use, and long-term administration has been associated with the development of fluoride excess and periostitis/exostoses.[93,94] Bone pain, elevated serum alkaline phosphatase levels, and periosteal elevation is observed on radiographic imaging, and bone scans may be useful to follow the course of disease.[95] Resolution of this manifestation occurs after cessation of voriconazole therapy.[96]

Therapeutic Drug Monitoring

TDM of voriconazole is recommended, given the poor dose-response relationship[89] and variability of patient serum drug levels in patients receiving standard dosing regimens.[97] The usual indications for TDM are poor clinical response or adverse events. Serum drug concentrations should be maintained between 1.0 and 5.5 μg/mL. Children are usually rapid metabolizers, requiring 6 to 8 mg/kg every 12 hours. Variability in children is sufficiently large that monitoring drug levels is essential. Japanese and some other non-Indian Asian populations have a high frequency of slow metabolizers and higher voriconazole levels due to frequency of the CYP2C19*2 genotype. CYP3A4 and CYP2C9 polymorphisms also affect voriconazole serum drug concentrations, but to a lesser degree.[98,99] It has been shown that voriconazole TDM does not impact the incidence of adverse events.[100] In contrast, a meta-analysis reported that patients with therapeutic concentrations were twice as likely to respond to treatment, and patients with supratherapeutic concentrations were four times as likely to experience toxicity.[101]

Clinical Use
Aspergillosis
Voriconazole is licensed in the treatment of invasive aspergillosis following a randomized multicenter trial comparing voriconazole with amphotericin B deoxycholate in the treatment of invasive aspergillosis. At week 12, significant differences were observed, with a successful outcome in 52% of patients in the voriconazole group compared with only 31% in the amphotericin B deoxycholate group.[102] The survival rates also were significantly different between groups (71% in the voriconazole group vs. 58% in the amphotericin B deoxycholate group). Efficacy in central nervous system aspergillosis[103] and other disseminated forms[104] has also been observed, showing the utility of voriconazole even in severe infections. Voriconazole has also been used successfully in noninvasive disease such as allergic bronchopulmonary aspergillosis.[105] Although offering potential advantages over itraconazole, including improved gastrointestinal tolerance and bioavailability, no comparative data are available.

Febrile Neutropenia
In an open-label randomized trial comparing voriconazole with liposomal amphotericin B for persistent fever in neutropenic patients, mortality was similar in both groups. In this study, the overall response was higher in patients treated with liposomal amphotericin B, although voriconazole was associated with fewer documented breakthrough fungal infections, fewer infusion reactions, and less nephrotoxicity.[106] The results of this study are controversial, and the results may have been affected by the open-label design. Empirical treatment with voriconazole during febrile neutropenia may be useful in select patients.

Other Mycoses
Voriconazole has additionally been used successfully in the treatment of other hyaline mold infections, although de novo resistance in these often difficult-to-treat mycoses can be seen. The treatment of these less common and often refractory fungal infections was evaluated in a prospective study, and 46% of fusariosis and 30% of scedosporiosis infections demonstrated a satisfactory response to voriconazole.[83] Voriconazole is also effective in the treatment of mucosal and invasive candidiasis,[83,107] although echinocandins remain first-line agents, and there is little benefit over fluconazole for most *Candida* infections.[12] Voriconazole has been shown to be effective as a prophylactic agent for allogeneic hematopoietic stem cell transplant recipients[53] and in the treatment of *Cryptococcus* and the endemic mycoses—although use in these settings typically follows failure or intolerance to other agents.[83] The phaeohyphomycoses frequently respond to voriconazole.[78] Although voriconazole exhibits a broad spectrum of activity, it is not useful in the treatment of mucormycosis and has poor activity against *Sporothrix* spp. in vitro.

POSACONAZOLE (NOXAFIL)
Formulations and Pharmacology
Posaconazole is available as a 100-mg delayed-release tablet, an oral suspension (40 mg/mL), and an IV formulation. The oral suspension requires a fed state or an acidic carbonated beverage to maximize bioavailability,[108] and saturable absorption with this formulation obviates once-daily dosing.[6] Gastric acid suppressants (H2 receptor antagonists and proton pump inhibitors) significantly decrease serum drug concentrations when administered with the oral suspension.[108] Bioavailability of the tablet formulation is not significantly affected by food or gastric acid. Posaconazole penetrates most sites well, although similar to itraconazole, CSF levels are generally not observed. Clinical experience with posaconazole in the treatment of central nervous system fungal infections is limited, although successful therapy has been observed.[109] The half-life of posaconazole is approximately 27 hours and allows for once-daily dosing with the IV or tablet formulation. The suspension formulation requires more frequent dosing due to decreased bioavailability, and these dosing differences between formulations have led to significant medication errors and prompted warning letters from both US and European regulatory agencies. Most of the drug is eliminated via the fecal route unchanged (77%), and urinary concentrations are negligible. Dose adjustment is not indicated in renal impairment or in Child-Pugh class A, B, or C liver disease.

Drug Interactions
Posaconazole undergoes hepatic metabolism via glucuronidation and has the capacity for drug-drug interactions through inhibition of CYP3A4 isoenzymes.[110] Posaconazole may also inhibit P-glycoprotein transporters, although a clinically relevant effect has not thus far been demonstrated. Concurrent administration with other medications known to prolong the QTc interval metabolized through CYP3A4 is relatively contraindicated. Coadministration with posaconazole may increase the levels of both cyclosporine and tacrolimus.

Side Effects
Adverse effects from posaconazole are primarily gastrointestinal, with nausea, vomiting, and diarrhea more frequent with the oral suspension.[111] Hepatotoxicity and cardiac toxicity due to prolongation of the QTc interval have also been described.[112] The IV formulation of posaconazole contains a cyclodextrin vehicle, and in the setting of renal dysfunction this solubilizing agent may accumulate, although this is of uncertain clinical significance. Hypokalemia, hypertension, and peripheral edema have also been described, with inhibition of 11β-hydroxylase and/or 11β-hydroxysteroid dehydrogenase by posaconazole suggested as the pathophysiologic mechanism.[111]

Therapeutic Drug Monitoring
TDM of posaconazole concentrations is recommended in most current Infectious Diseases Society of America guidelines.[12,113] The tablet formulation has significantly improved drug exposure compared with the solution, and drug levels have correlated with both prophylaxis and treatment efficacy[114,115]; however, toxicity may also be associated with high drug concentrations.[116] Target serum levels are not well defined; however, levels >0.7 μg/mL for prophylaxis and >1.0 μg/mL for treatment are generally recommended. Genetic polymorphisms have not been found to affect posaconazole pharmacokinetics.[117]

Clinical Use
Prophylaxis in High-Risk Patients
Posaconazole decreases the incidence of fungal infections in high-risk patients during graft-versus-host disease following allogeneic bone marrow transplantation.[52] In this study posaconazole was compared with fluconazole for antifungal prophylaxis in severe graft-versus-host disease and was found to be superior to fluconazole in the prevention of invasive aspergillosis (2% vs. 7%) and in prevention of death due to fungal infections (1% vs. 4%). Treatment-related adverse events were comparable between groups (36% vs. 38%). Similarly, posaconazole prophylaxis was compared with fluconazole or itraconazole in patients with neutropenia following chemotherapy (acute myelogenous leukemia or myelodysplastic syndrome).[51] Posaconazole was more effective in prevention of invasive fungal infections than either fluconazole or itraconazole (2% vs. 8%), in prevention of aspergillosis (1% vs. 7%), and in overall mortality (16% vs. 22%). More adverse events occurred in the posaconazole group.

Other Mycoses
Posaconazole has been evaluated in a comparative study with fluconazole in the treatment of oropharyngeal candidiasis in patients with HIV/AIDS and found to be equally effective. Clinical relapse was less common in the group treated with posaconazole.[118] Posaconazole has also been effectively used in a number of other invasive mycoses, including refractory aspergillosis,[114] fusariosis,[119] eumycetoma, chromoblastomycosis,[120] and the phaeohyphomycoses.[78] Additionally, posaconazole is a useful agent in the treatment of coccidioidomycosis[121] and histoplasmosis,[122] although data in the treatment of other endemic mycoses are limited. Following improvement with a polyene, posaconazole is often used as oral step-down therapy during treatment of the mucormycoses.[123]

ISAVUCONAZOLE (CRESEMBA)
Formulations and Pharmacology
Isavuconazonium sulfate (referred to in this chapter as isavuconazole) is available in both an oral capsule (100 mg of isavuconazole) and an IV formulation; the IV formulation does not contain cyclodextrin. Loading doses are required over the initial 48 hours of therapy.

Isavuconazole has a prolonged half-life (approximately 130 hours), which allows once-daily dosing. Oral capsules are well absorbed with a bioavailability of approximately 98% and can be taken with or without food. The isavuconazonium sulfate prodrug is rapidly hydrolyzed in the blood to isavuconazole and an inactive cleavage product by serum esterases, predominately butylcholinesterase. Isavuconazole is widely distributed through body tissues with a steady-state volume of distribution of approximately 450 L and a prolonged half-life of 130 hours. Central nervous system infections have limited available data, but isavuconazole has been useful in the treatment of a few reported patients with cryptococcal and coccidioidal meningitis.[124,124a] Less than 1% of isavuconazole is present in the urine. Dose adjustment is not indicated in renal impairment or in Child-Pugh class A or B liver disease.

Drug Interactions

Significant interactions with drugs metabolized by CYP occur, especially with substrates and inducers of the CYP3A4 enzyme, although preclinical studies and limited clinical data suggest these drug interactions may be less severe than with other triazole agents. Coadministration of methotrexate with isavuconazole increases exposure to 7-hydroxymethotrexate, a potentially toxic metabolite. Tacrolimus and sirolimus levels are likely to be increased by coadministration of isavuconazole, whereas interactions with cyclosporine and glucocorticoids appear to be modest.

Side Effects

The most commonly observed adverse effects are nausea, vomiting, diarrhea, headache, elevated transaminases, and hypokalemia. Overall drug-related side effects in patients receiving isavuconazole are less frequent than in patients receiving voriconazole. In contrast to the other triazoles, isavuconazole is associated with QTc shortening, and although the clinical significance of this remains unclear, it may be useful in patients receiving multiple other QTc prolonging medications.

Therapeutic Drug Monitoring

No definitive recommendations have been made for or against isavuconazole TDM, and clinical experience continues to accumulate. Further studies are needed to clarify whether elevated isavuconazole levels are associated with toxicity and whether TDM is indicated with either the oral or the IV formulation.

Aspergillosis and Mucormycosis

Isavuconazole has been evaluated in a prospective comparative trial with voriconazole in the primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi.[125] In this study, isavuconazole was found to be noninferior to voriconazole in clinical efficacy measured by survival and composite clinical responses, but with a lower incidence of drug-related adverse events (42% vs. 60%). In a single-arm open-label trial, isavuconazole was evaluated in the treatment of mucormycosis and other rare fungi, including the endemic mycoses.[126] Overall, isavuconazole showed activity against mucormycosis and was considered to have similar efficacy compared with historical patients treated with amphotericin B. Of the 18 patients with proven mucormycosis initially treated with isavuconazole, 3 had a complete response, 3 had a partial response, and 15 failed or had the drug discontinued. Additional data are needed.

Other Use

Isavuconazole (IV followed by oral therapy) was also compared with caspofungin followed by oral voriconazole in the treatment of candidemia/invasive candidiasis.[127] In this study a successful response to therapy was observed in only 60% of patients in the isavuconazole arm and 71% in the caspofungin arm—findings confirming the superiority of echinocandins as first-line therapy for invasive candidiasis, as seen in other studies.[128] A limited number of patients with cryptococcosis, paracoccidioidomycosis, coccidioidomycosis, histoplasmosis, and blastomycosis have been evaluated with isavuconazole; although the results are generally favorable, additional data are warranted.[124]

INVESTIGATIONAL AGENTS

Albaconazole, ravuconazole, and non-azole inhibitors of lanosterol 14α-demethylase are currently in various stages of development and may offer advantages over existing antifungals. A new itraconazole formulation (SUBA-itraconazole) has been recently approved and has enhanced oral absorption compared with the liquid or capsule forms.[129] Multiple clinical trials evaluating this new formulation are currently ongoing.

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The complete reference list is available online at Expert Consult.

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40C Antifungal Drugs: Echinocandins

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SHORT VIEW SUMMARY

- Echinocandins are semisynthetic cyclic lipopeptides that exert fungicidal activity against most *Candida* spp. and fungistatic activity against *Aspergillus* spp. by inhibiting the synthesis of cell-wall (1→3)-β-D-glucan.
- Three echinocandins are currently on the market: caspofungin, anidulafungin, and micafungin. Another echinocandin, rezafungin, and a nonechinocandin, the (1→3)-β-D-glucan synthase inhibitor ibrexafungerp, currently are in clinical trials.
- Echinocandins are agents of choice for treatment of candidemia and many other types of deeply invasive candidiasis, and as salvage or combination agents for treatment of invasive aspergillosis. They also have roles in empirical treatment of febrile neutropenia and as antifungal prophylaxis against invasive candidiasis in hematopoietic stem cell transplant recipients and invasive fungal infections after liver transplantation and surgery.
- Half-lives range from 9 to 11 hours for caspofungin, 11 to 17 hours for micafungin, and 24 to 26 hours for anidulafungin. Each of the drugs is dosed intravenously once daily, without need for renal dose adjustment.
- Drug-drug interactions are minimal, and safety profiles are excellent.
- Echinocandin resistance rates are low in general but may be encountered in up to 10% of *Candida glabrata* at high-risk centers. Resistance rates among *Candida auris* isolates are ≈3% to 5%.
- Caspofungin minimum inhibitory concentrations and interpretive breakpoints may overcall *Candida* resistance; anidulafungin or micafungin resistance is an accurate proxy for the class.

The echinocandins are semisynthetic lipopeptides that have emerged as agents of choice for the treatment of many infections by *Candida* spp., salvage and combination agents in the treatment of invasive aspergillosis, empirical treatment options during febrile neutropenia, and empirical or prophylactic agents in patients suspected of, or at, increased risk for invasive fungal infections.[1–5] Echinocandins noncompetitively inhibit (1→3)-β-D-glucan synthase, an enzyme complex that is essential for the synthesis of (1→3)-β-D-glucan, the backbone of the cell wall in ascomycetous fungi. Mammalian cells lack a cell wall, and the target specificity of the echinocandins may help account for reduced toxicity, fewer side effects, and diminished drug-drug interactions compared with earlier classes of systemic antifungals, such as polyene (amphotericin B) or azole agents.[1] Three echinocandins are currently available for clinical use. Caspofungin (Cancidas; Merck, Kenilworth, NJ), micafungin (Mycamine; Fujisawa Healthcare, Osaka, Japan), and anidulafungin (Eraxis; Pfizer, New York, NY) were approved by the US Food and Drug Administration (FDA) in 2001, 2005, and 2006, respectively.[4] Although there are physiochemical and pharmacokinetic differences among these agents, they exhibit almost identical spectra of activity, and practice guidelines generally consider them to be interchangeable.[6,7] In a direct comparison of caspofungin versus micafungin for the treatment of invasive candidiasis, treatment responses were indistinguishable.[8]

This chapter will review the spectra of activity, pharmacology, susceptibility and resistance patterns, and clinical roles of the currently available echinocandins in detail. In a short concluding section, consideration will be given to the newer echinocandin rezafungin (formerly known as CD101; Cidara, San Diego, CA) and the nonechinocandin (1→3)-β-D-glucan synthase inhibitor ibrexafungerp (formerly known as SCY-078; Scynexis, Jersey City, NJ), which are under investigation in clinical trials.[3]

STRUCTURE, MECHANISM OF ACTION, AND SPECTRUM OF ACTIVITY

Caspofungin, micafungin, and anidulafungin have cyclic lipopeptide core structures derived from pneumocandin A_o or pneumocandin B_o that confer antifungal activity (Fig. 40C.1). Side-chain modifications in each of the agents have little effect on antifungal activity compared with parent compounds but improve aqueous solubility.[9–11] The echinocandins bind to the Fks catalytic subunit of (1→3)-β-D-glucan synthase. The resulting inhibition of (1→3)-β-D-glucan synthesis causes an increase in cell-wall permeability and disturbances of intracellular osmotic pressure.[12] The extent of activity against various fungi is determined by cell-wall glucan content. The potency of echinocandins in vivo may be augmented by immunomodulatory activity stemming from unmasking or release of cell-wall glucans, leading to dectin-1 receptor activation of phagocytes and enhanced fungal killing.[13–15]

Echinocandins exert fungicidal activity against *Candida* and *Saccharomyces* spp. by causing cell lysis,[16–18] and they are also the most active class of antifungal agents against *Candida* biofilms in vitro and in animal models.[19–21] Each of the currently approved agents exhibits prolonged postantifungal effects against *Candida,* which are of unclear significance in vivo.[4,22] There is a hierarchy of activity against *Candida* spp., as the lowest minimum inhibitory concentrations (MICs) and most robust effects in animal models are evident against *C. albicans, C. glabrata, C. tropicalis, C. krusei,* and *C. dubliniensis*.[1] *C. parapsilosis* carries an Fks polymorphism that results in decreased echinocandin affinity and higher MICs than observed for the species listed earlier.[1] Echinocandins appear to be fungistatic rather than fungicidal against *C. guilliermondii* and *C. lusitaniae*.[2,23] Breakthrough *C. parapsilosis* infections among patients receiving an echinocandin are well reported,[24,25] although clinical trials of each of the agents show equivalent outcomes for *C. parapsilosis* and *C. albicans* infections. Furthermore, conclusive evidence of poorer outcomes for treatment of *C. guilliermondii* or *C. lusitaniae* infections in clinical trials is lacking. Mouse model data support clinical findings that echinocandins can be used to treat *C. parapsilosis* infections successfully, despite higher MICs than against other species.[26] In vitro susceptibility and mouse model data indicate that echinocandins are the most consistently active class of antifungals against the emerging pathogen *C. auris*.[27]

In general, echinocandins are fungistatic against *Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus,* and *Aspergillus niger*, the most common causes of invasive aspergillosis in humans.[1,28] Antifungal activity

correlates with morphologic changes and inhibition of growth at hyphal tips, but viable fungi may remain in tissue.[29–31] Echinocandins have excellent activity against the cyst form of *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*), suggesting a potential role in prophylaxis against *Pneumocystis* pneumonia.[28] Micafungin and anidulafungin were active against *P. jirovecii* during mouse and rat infections,[32,33] but clinical data in humans are limited. Echinocandins are inactive against *Cryptococcus neoformans* and *Trichosporon* spp., in which (1→6)-β-D-glucan, rather than (1→3)-β-D-glucan, predominates in the cell wall.[1,2] Agents are also not reliably active against the yeast forms of endemic mycoses, or Mucorales, *Fusarium* spp., *Scedosporium* spp., and other non-*Aspergillus* molds that have diminished (1→3)-β-D-glucan synthase activity.[2]

PHARMACOLOGY

Pharmacokinetic properties of the commercially available echinocandins are summarized in Table 40C.1. In general, echinocandin pharmacokinetics are similar in bone marrow and peripheral blood stem cell transplant recipients, patients with hematologic malignancies, critical care unit residents, and patients undergoing continuous venovenous hemodialysis.[34–39] Drug clearance may be higher in obese patients and those with candidemia or other forms of invasive candidiasis, but these covariates account for a minority of interpatient variability in pharmacokinetics.[34,40]

Caspofungin, micafungin, and anidulafungin have poor oral bioavailability and are only available in intravenous (IV) formulations.[1] They exhibit linear concentration-dose relationships, although caspofungin may accumulate as doses increase.[41] Each of the agents is highly protein bound in plasma. After initial distribution, caspofungin and micafungin are taken up by the liver and red blood cells (the latter for micafungin only), where they are slowly degraded to inactive metabolites that are largely excreted via bile.[1] Anidulafungin is degraded almost entirely in plasma rather than the liver. The agents distribute well into tissues such as liver, spleen, lungs, and kidneys, but their large molecular weights and high protein binding limit penetration into urine, cerebrospinal

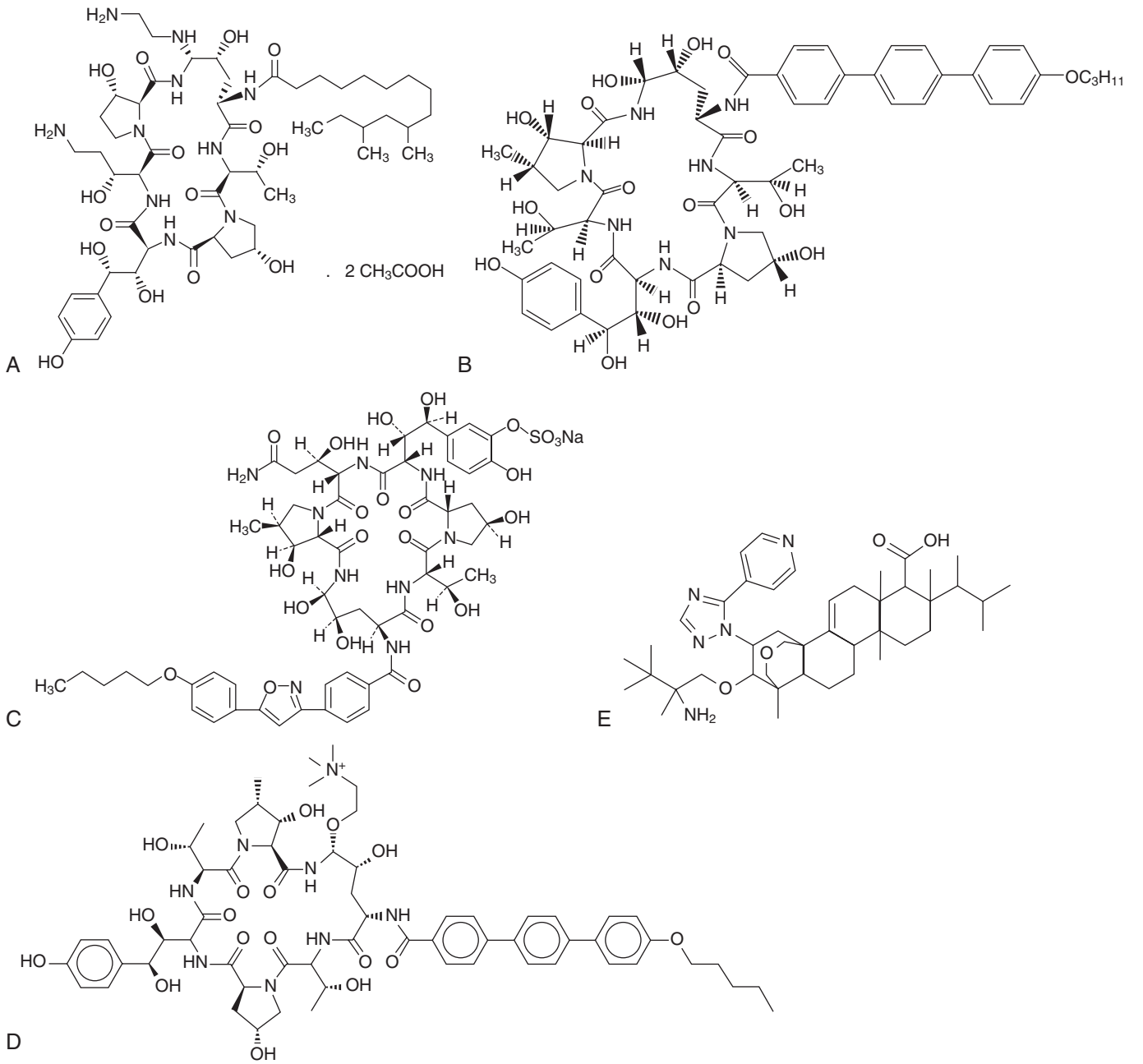

FIG. 40C.1 Structures of echinocandins and ibrexafungerp. Shown are caspofungin (A), anidulafungin (B), micafungin (C), rezafungin (D), and ibrexafungerp (E).

TABLE 40C.1 Echinocandin Pharmacokinetic Parameters

PARAMETER	CASPOFUNGIN	ANIDULAFUNGIN	MICAFUNGIN
Oral bioavailability	<10%	2–7%	<10%
$T_{1/2}$ (hours)	9–11	24–26	11–17
Protein binding (%)	96–97	84–99	≥99
Metabolism	Slow peptide hydrolysis and *N*-acetylation; spontaneous degradation to inactive product	Not metabolized; slow degradation to inactive metabolites	Catechol-*O*-methyltransferase pathway
Elimination	35% in feces, 41% in urine	Primarily in feces, 1% in urine	40% in feces, <15% in urine
Plasma clearance (mL/min)	10–12.5	16.67	10.5
CSF penetration	Low	<0.1%	Low
Renal dose adjustment	None	None	None
Hepatic dose adjustment	None for mild dysfunction (Child-Pugh 5–6); reduce maintenance dose to 35 mg/d for moderate dysfunction (Child-Pugh 7–9); no data for severe dysfunction	None	None for moderate dysfunction (Child-Pugh 7–9); no data for severe dysfunction
C_{max} (mg/L) (50-mg single dose)	7.64	2.07–3.5	4.95
Steady-state AUC_{0-24} (μg/h per mL (70-mg single dose)	87.9–114.8	42.3–53	111.3

AUC_{0-24}, 24-hour area under the (plasma) concentration-time curve; *C_{max}*, maximum concentration; *CSF*, cerebrospinal fluid; *$T_{1/2}$*, elimination half-life.

TABLE 40C.2 Echinocandin Drug Interactions

INTERACTING DRUG	CASPOFUNGIN	ANIDULAFUNGIN	MICAFUNGIN
Tacrolimus	Tacrolimus AUC, peak and 12-h concentrations decreased ≈20%	No significant effect	No significant effect
Sirolimus	No data	No data	Sirolimus AUC increased 21%
Cyclosporine	Caspofungin AUC increased ≈35%	Anidulafungin AUC increased 22%	Cyclosporine clearance decreased 16%
Nifedipine	No data	No data	Nifedipine AUC increased 18%
Rifampin	Caspofungin steady-state concentrations decreased	No significant effect	No significant effect
Voriconazole	No data	No significant effect	No significant effect

AUC, Area under the (plasma) concentration-time curve.

fluid, brain, prostate, and (with the exception of micafungin) ocular fluid. Despite attaining low concentrations in urine, echinocandins have been reported to sterilize azole-resistant candiduria in several case reports,[42–44] and they have been used successfully in experimental models of renal candidiasis.[45] Pharmacokinetic modeling in mice demonstrated that echinocandins accumulated within the kidneys and other organs, which served as reservoirs from which biologically active drug slowly returned to the bloodstream.[46,47] Tissue persistence correlated with ongoing antifungal activity, even after serum concentrations decreased below the MIC.

Elimination half-lives range from 9 to 11 hours for caspofungin, 11 to 17 hours for micafungin, and 24 to 26 hours for anidulafungin; each of the drugs is dosed once daily.[1] Standard doses are as follows: anidulafungin (200-mg loading dose, followed by 100 mg daily; 100-mg loading dose, followed by 50 mg daily for treatment of esophageal candidiasis), caspofungin (70-mg loading dose, followed by 50 mg daily; 50 mg daily for treatment of esophageal candidiasis), and micafungin (100 mg daily; 150 mg for treatment of esophageal candidiasis; 50 mg daily as prophylaxis). IV infusions are typically administered slowly over at least 1 hour to avoid histamine-mediated or histamine-like reactions.[4] No renal dose adjustments are necessary, and the drugs are not dialyzed. Hepatic dose adjustments are not needed for anidulafungin. Dose reductions of caspofungin, but not micafungin, are recommended for moderate hepatic dysfunction; data are lacking for both agents in severe hepatic dysfunction. In general, the echinocandins are well tolerated and similar in types of adverse events. Infusion-related reactions, thrombophlebitis, and mild gastrointestinal (GI) symptoms may occur in <5% of patients.[41] None of the agents are major substrates, inducers, or inhibitors of CYP450 enzymes or the P-glycopeptide transport system, and drug interactions are minimal. The most notable drug interactions are listed in Table 40C.2.

The echinocandins exhibit concentration-dependent fungicidal activity against *Candida* spp. in vivo.[26,48–50] The pharmacokinetic-pharmacodynamic parameters that best correlate with treatment efficacy in mouse models and human studies of candidiasis are the maximum concentration–to-MIC (C_{max}/MIC) ratio or area under the plasma concentration-time curve–to-MIC (AUC/MIC) ratio.[26,45,48–51] Exposure-response relationships for each echinocandin in a study of mice with hematogenously disseminated candidiasis partitioned into fungistatic and fungicidal components at lower and higher doses, respectively.[52] Dosing regimens that mimicked pharmacokinetics in humans receiving currently recommended treatment regimens resulted in fungistatic rather than fungicidal activity.

The pharmacokinetic-pharmacodynamic parameter that best correlates with the fungistatic activity of echinocandins against *Aspergillus* spp. appears to be C_{max}/MIC,[2] although data are less extensive than that against *Candida* spp.

SUSCEPTIBILITY TESTING IN VITRO

Clinicians should be aware of several issues surrounding echinocandin susceptibility testing. Reference broth microdilution methods for testing echinocandins against *Candida* and *Aspergillus* spp. have been developed by the Clinical Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST).[53,54] There is good interlaboratory agreement in anidulafungin and micafungin MICs determined by these methods against *Candida* and *Aspergillus* isolates.[53–56] In an international study, however, modal caspofungin MICs generated by individual laboratories using either of the reference methods differed by more than four twofold dilutions against *C. albicans, C. glabrata*, *C. tropicalis,* and *C. krusei*.[56] Interlaboratory variability in MICs is most striking for caspofungin against *C. glabrata*.[54,55]

Most hospitals do not use reference broth microdilution methods but rather commercialized assays, such as Sensititre YeastOne (SYO, Trek Diagnostics, Cleveland, OH) and Etest (bioMérieux, Marcy-l'Étoile, France), or automated systems such as Vitek 2 (bioMérieux).[55,57] Anidulafungin and micafungin MICs generated by these methods demonstrate good essential agreement (MICs within a twofold dilution) with those from reference methods against both *Candida* and *Aspergillus*. The commercialized assays also exhibit less interlaboratory disagreement in caspofungin MICs against *Candida*.[58,59] Nevertheless, interpretive breakpoints applied to MICs from these tests may assign disproportionately high rates of caspofungin nonsusceptibility among *C. glabrata* and *C. krusei* isolates, compared with other agents.[60,61] For this reason it has been proposed that anidulafungin or micafungin MICs and susceptibility interpretations against *Candida* be used as proxies for the echinocandin class, rather than relying upon caspofungin MICs.[62] Clinicians should know how echinocandin susceptibility and resistance are tested and defined for *Candida* and *Aspergillus* isolates from their centers. To place MIC results in some context, institutional MIC and resistance patterns for all agents should be compared with those published in the literature.[54] It is also important to recognize that clinical breakpoints proposed by CLSI and EUCAST for certain *Candida* and *Aspergillus* spp. may differ. Clinicians are advised to consult periodically with their clinical microbiology laboratories and review the latest documents from the respective agencies. Suggestions for incorporating echinocandin susceptibility testing into routine clinical practice are offered in the following section on echinocandin resistance.

Echinocandins are well known to demonstrate paradoxical effects in vitro against certain *Candida* and *Aspergillus* isolates, in which growth is inhibited at the MIC but increased at concentrations greater than the MIC. Paradoxical effects have been demonstrated against *C. albicans, C. parapsilosis, C. krusei, C. tropicalis, C. dubliniensis*, and *C. auris* isolates,[22,27,63–70] as well as *A. fumigatus*, *A. flavus*, and *A. terreus*.[71] Each of the commercially available agents has been implicated, but reports are most common for caspofungin. The precise mechanisms accounting for paradoxical effects are unknown but likely involve activation of cell-wall integrity regulatory pathways and upregulated chitin synthesis to compensate for reduced (1→3)-β-D-glucan.[70,72] The majority of studies using mouse models have failed to validate paradoxical growth in vivo.[64,67] In a recent study *C. auris* isolates exhibiting paradoxical growth in the presence of elevated caspofungin concentrations in vitro responded as if fully susceptible in a mouse model of hematogenously disseminated candidiasis.[27] Moreover, paradoxical growth in vitro is eliminated in human serum, and poorer outcomes were not reported among patients receiving higher echinocandin doses in clinical trials. Therefore the phenomenon is likely to be of minimal clinical significance.[8,73]

ECHINOCANDIN RESISTANCE

With increased use of the echinocandins, reports have documented the emergence of resistance.[54,61,74–76] Resistance is most common among *C. glabrata* isolates and remains significantly less common for most other *Candida* and *Aspergillus* spp.[54,77] Diminished susceptibility is mediated by mutations in hot spots of *FKS* genes, with specific mutations conferring higher or lower levels of resistance.[54,77–79] Echinocandin inhibition of (1→3)-β-D-glucan synthase is reduced by 30- to several thousand-fold in isolates harboring various *FKS* mutations.[80–82] Many of these mutations correlate with poor treatment responses in mouse models of disseminated candidiasis.[50,83–85] Selection of resistance mutations in vitro occurs at highest frequency for caspofungin, followed by anidulafungin and micafungin.[86] For the most part mutations confer resistance to all three agents. Agent-specific mutations have been reported,[87] but the clinical relevance of these findings or mutational frequency rates in vitro has not been established.[54]

At some large centers ≈10% of *C. glabrata* strains recovered from sterile sites are *FKS* mutants.[54,60,61,74,75,88] Rates among *C. glabrata* in strain biorepositories are much lower.[54] Molecular resistance typically is seen in the setting of extensive prior echinocandin exposure.[54,60,61,76,88] Particularly worrisome is the emergence of *C. glabrata* isolates that are resistant to both fluconazole and echinocandins, as reported for 12% to 14% of fluconazole-resistant isolates at several centers.[54] Overall echinocandin resistance rates among *C. auris* isolates are ≈3% to 5%, although these may be higher for isolates in some geographic regions.[27,89–91] Echinocandin resistance in *C. auris* invariably is associated with multidrug resistance, as fluconazole and amphotericin B resistance rates are ≥80% and ≈30%, respectively.[89–93]

FKS mutations most often arise in specific settings, in which echinocandin resistance rates are significantly higher than in the broader population with invasive candidiasis. The greatest risk is among patients who develop breakthrough infections during echinocandin treatment, in whom ≥50% of *C. glabrata* or *C. albicans* isolates harbor mutations.[54,94,95] In contrast, *FKS* mutant isolates account for <10% of *C. glabrata* or *C. albicans* infections among patients with remote echinocandin exposure[61]; risk is greatest for prolonged prior exposure and exposure within the preceding month.[54,75] Other risk factors for *FKS* mutant *C. glabrata* isolates include underlying GI disorders, solid-organ transplantation, and recurrent invasive candidiasis.[54,74,75,95] Intraabdominal candidiasis can represent a hidden reservoir for echinocandin resistance at centers that only test bloodstream *Candida* isolates.[95] The detection of *FKS* mutations may be a more reliable predictor of echinocandin treatment failures than elevated MICs in patients with invasive candidiasis, but most clinical microbiology laboratories do not have the capacity to conduct rapid molecular testing.[88,96] An elevated echinocandin MIC in the presence of prior drug exposure is a useful surrogate for the presence of an *FKS* mutation.[54,76,88] In the end, most echinocandin treatment failures are not due to drug resistance but, rather, a combination of factors, such as underlying disease, host immune function, severity of illness, source control, time to initiation of treatment, pharmacokinetic-pharmacodynamic parameters at the site of infection, and isolate fitness.[54,97]

In consideration of the issues raised in the previous paragraph, echinocandin susceptibility testing and/or screening for *FKS* mutations is not likely to be necessary in managing most patients with invasive fungal infections.[54] Such testing may be most useful for the subset of patients with infections that occur during echinocandin exposure or after prolonged remote drug exposure, among patients failing to respond to treatment, and in those infected by *C. glabrata* and *C. parapsilosis*.[7,54] Routine susceptibility testing is important to establish the epidemiology of resistance locally and as a sentinel for detecting increasing rates of resistance.

CLINICAL INDICATIONS

Candidiasis

Echinocandins exert greater anti-*Candida* activity than fluconazole in vitro and in animal models of candidiasis,[98] and they are less toxic and better tolerated than amphotericin B formulations.[99,100] In humans echinocandins are most useful in the treatment of candidemia and invasive candidiasis, as established in a series of randomized, blind, controlled trials. Regardless of the comparator agent in the trials, success rates for the echinocandins were similar to each other.[8,100–103] Individual studies, powered for noninferiority, have shown echinocandins to be comparable to fluconazole, amphotericin B deoxycholate, and liposomal amphotericin B.[8,100–103] In one prospective, randomized, blind, controlled trial, anidulafungin was superior to fluconazole for patients with candidemia and invasive candidiasis, as measured by clinical and microbiologic success at completion of treatment (76% vs. 60%; 95% confidence interval [CI], 3.9 to 27; $P = .01$).[103] A reinterpretation of data excluding the highest enrolling center (which reported exaggerated differences in response between the groups) revealed global response rates of 73% and 61%, respectively (CI, −1.1 to 25.3). Statistical superiority for anidulafungin in the overall cohort was also lost by 6-week follow-up. A patient-level review of data pooled from seven randomized antifungal trials against invasive candidiasis found that echinocandin treatment was associated with significantly improved survival and greater clinical success rates than treatment with an amphotericin B formulation or azole (mortality rates: 27%, 35%, and 36%, respectively; $P < .0001$ for echinocandin vs. others).[100] In subgroup analysis, improved outcomes were evident for patients infected with *C. albicans* and non–*C. albicans* spp.

The latest clinical practice guidelines from the Infectious Diseases Society of America (IDSA) recommend an echinocandin as the preferred initial agent for treatment of candidemia in both neutropenic and

nonneutropenic patients, and for empirical treatment of suspected invasive candidiasis in intensive care unit patients.[7] If patients with documented candidiasis demonstrate a clinical response to an echinocandin, guidelines indicate that step-down therapy with fluconazole can be used to complete a treatment course, usually beginning after 5 to 7 days if patients are infected with an isolate that is known or likely to be fluconazole susceptible. Published experience with echinocandins against deep-seated candidiasis is less extensive than for candidemia, and echinocandins may be limited by pharmacokinetic considerations in the treatment of diseases such as endophthalmitis, meningitis, and urosepsis.[104] Treatment guidelines for intraabdominal candidiasis recommend that antifungal choices follow the considerations laid out for candidemia, with echinocandins as appropriate first-line agents. Antifungal therapy is an adjunct to prompt source control in treatment of intraabdominal candidiasis.[105,106] An echinocandin is endorsed by IDSA as an alternative to amphotericin B formulations for frontline treatment of *Candida* endocarditis and chronic disseminated (hepatosplenic) candidiasis. The most recent IDSA guidelines no longer favor fluconazole over an echinocandin for treatment of *C. parapsilosis* infections, as was recommended previously.[6]

All three echinocandins achieved response rates similar to fluconazole in trials against esophageal candidiasis, but relapse rates were greater, with the exception of high-dose micafungin, which was comparable to fluconazole.[107–109] These findings and the availability of fluconazole as an oral formulation establish the echinocandins as second-line agents against mucosal candidiasis.

Aspergillosis

Treatment guidelines do not endorse echinocandins as primary treatment options against invasive aspergillosis.[110] Most reports of echinocandin treatment of invasive aspergillosis have been salvage studies of patients unable to tolerate or not responding to other antifungal agents, or studies of combination antifungal regimens. In salvage settings most data are for caspofungin, followed by micafungin. In general, the agents were safe, and response rates have ranged from about 40% to 50%.[111–115] Dose escalation studies have shown echinocandins to be well tolerated at higher-than-conventional doses,[111] and it has been proposed that such regimens could prove more effective in treating invasive aspergillosis.[116] There are no data to support this practice, but administration of large doses would be consistent with optimizing C_{max}/MIC, the pharmacokinetic-pharmacodynamic predictor of responses in experimental systems.[2]

Data from in vitro and mouse model experiments have demonstrated synergy between echinocandins (as cell wall–active agents) and mold-active azoles or amphotericin B (as cell membrane–active agents) against *Aspergillus*.[116,117] In keeping with these findings, improved outcomes have been reported in retrospective, single-center studies of patients with aspergillosis who were treated with an echinocandin and an azole or amphotericin B.[118–124] In a randomized, double-blind, placebo-controlled multicenter trial of voriconazole plus anidulafungin (the latter given for the first 2 weeks of treatment) versus voriconazole monotherapy in hematologic malignancy or hematopoietic stem cell transplant patients, there was a nonsignificant trend toward reduced mortality in the combination arm (16% vs. 27%; $P = .09$).[121] Toxicity was not increased with the combination regimen. Although there is no conclusive benefit for combination therapy, IDSA guidelines recommend considering an echinocandin plus voriconazole for the initial stage of primary therapy in the setting of severe disease, especially in patients with hematologic malignancies and those with profound and persistent neutropenia.[110]

Empirical Treatment of Febrile Neutropenia and Antifungal Prophylaxis

Empirical antifungal therapy reduces invasive fungal infection-related mortality among patients with febrile neutropenia who have not responded to antibacterial agents.[125] Several trials have demonstrated that echinocandins are effective and well tolerated in this setting.[126–130] In a recent meta-analysis echinocandins were the most effective class of antifungal agents for empirical treatment of febrile neutropenia, as assessed by mortality and treatment responses.[125] Echinocandins also have been shown to be effective as antifungal prophylaxis against invasive candidiasis after hematopoietic stem cell transplantation[131] and against invasive fungal infections after liver transplantation and surgery.[132–136]

NEW AGENTS: REZAFUNGIN AND IBREXAFUNGERP

Rezafungin is a novel long-acting echinocandin that is stable in plasma and aqueous solution. It is under evaluation as a once-weekly IV formulation.[3] Phase I dose escalation data did not show serious adverse events or safety concerns and confirmed low clearance (<0.28 L/h), long plasma half-life (>80 hours), and minimal excretion.[137] Rezafungin has activity comparable to other echinocandins against *C. albicans, C. glabrata, C. tropicalis*, *C. krusei*, *C. parapsilosis,* and *C. auris*, and it remains effective against some, but not all, *FKS* mutant isolates.[138] Rezafungin is active against *A. fumigatus, A. terreus, A. niger,* and *A. flavus*,[53] and mouse studies have demonstrated protection against *Pneumocystis* pneumonia.[3] Preliminary in vitro data using spontaneous resistance and serial passage–selection methodologies showed that *Candida* spp. develop low-level resistance to rezafungin similar to other echinocandins; passage did not select unique resistance-gene mutations.[139] In a mouse model of intraabdominal infection due to *C. albicans,* rezafungin penetrated the necrotic cores of abscesses significantly better than micafungin.[140] As of this writing the agent was under investigation in a phase III clinical trial for treatment of candidemia and invasive candidiasis, with plans for a phase III clinical trial as prophylaxis in allogeneic bone marrow transplant recipients. In the setting of prophylaxis the activity of rezafungin and other echinocandins against *P. jirovecii* cysts may complement anti-*Candida* and anti-*Aspergillus* activity. Plans for developing a topical application against acute vulvovaginal candidiasis were discontinued after release of unfavorable phase II clinical trial data.

Ibrexafungerp is not an echinocandin but, rather, a semisynthetic derivative of the natural product enfumafungin (a terpenoid and potent inhibitor of [1→3]-β-D glucan synthase). The agent has broad activity against *Candida* spp.,[141,142] including echinocandin-resistant isolates, *C. auris*, and *Aspergillus* spp.[141] As of this writing it is under investigation or scheduled for investigation in phase II and III clinical trials of refractory invasive fungal infections, invasive candidiasis, combination therapy of invasive aspergillosis, and acute and chronic vulvovaginal candidiasis. The agent is being developed in both IV and oral formulations. The latter may facilitate step-down therapy after an initial IV course of ibrexafungerp or an echinocandin. A cyclodextrin-based IV formulation of ibrexafungerp was placed on clinical hold by the FDA in 2017 after thrombotic events in a phase I trial. Clinical trials were scheduled to be reinitiated with a liposomal IV formulation in the latter half of 2018.

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The complete reference list is available online at Expert Consult.

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40D Antifungal Drugs: Flucytosine

Benjamin Colton

SHORT VIEW SUMMARY

- Flucytosine is a fluorinated pyrimidine analogue. The antifungal activity of flucytosine is due to its role as a subversive substrate within the pyrimidine salvage pathway, resulting in inhibition of both protein and DNA synthesis.
- Activity is primarily restricted to candidiasis and cryptococcosis, used in combination with amphotericin B.
- Dosage is 25 to 37.5 mg orally every 6 hours in patients with normal renal function. Blood levels should be monitored in azotemic patients and maintained below 100 μg/mL.
- Flucytosine is well absorbed orally, is eliminated by renal excretion, and penetrates well into cerebrospinal fluid, urine, and other body fluids.
- Toxicities include leukopenia, thrombocytopenia, and colitis, largely related to elevated drug levels. Hepatotoxicity also occurs but is less clearly dose related.

The search for new therapies in the pursuit of a cure for cancer has resulted in many failed chemotherapeutics. Despite falling short of their primary intent, many of these therapies have proven far more capable in fields outside oncology, including infectious diseases. One notable example of this is flucytosine. While attempting to leverage the profound biologic effects of substituting fluorine for hydrogen for the purpose of formulating new chemotherapies, Duschinsky and colleagues synthesized 12 fluoropyrimidines in the research laboratory of Hoffman-La Roche in 1957.[1] As with many pharmaceutical pursuits, only two of these compounds, 5-fluorouracil and 5-fluorocytosine (i.e., 5-flucytosine or flucytosine), would prove of clinical utility. Initial investigations into the activity of both agents by Drs. Duschinsky and Heidelberger reported appreciable antitumor and antibacterial effects for 5-fluorouracil, while noting 5-fluorocytosine's antitumor and antibacterial activity was markedly less.[2] While these early findings proved flucytosine to be a poor antineoplastic agent, its antifungal activity prompted further investigation.[3,4] Following evidence of flucytosine's in vitro and in vivo activity, several investigators set forth to elucidate the mechanism by which it exerted its selective antifungal activity.

PHARMACOLOGY

Flucytosine is a fluoropyrimidine, similar to cytosine and fluorouracil (Fig. 40D.1) The fluoropyrimidines exert their microbiologic activity by serving as subversive substrates within the pyrimidine salvage pathway. In order to accomplish this, flucytosine must first be taken up by fungal cells by the energy-dependent transporter, cytosine permease (Fig. 40D.2).[5] Cytosine permease also serves as the transporter for adenine, hypoxanthine, and cytosine, all of which competitively antagonize the uptake of flucytosine.[6] Once in the fungal cytoplasm, flucytosine is readily deaminated to 5-fluorouracil by cytosine deaminase.[7] The absence of cytosine deaminase in mammalian cells is fundamental to the antifungal selectivity and relative safety observed in humans.[8] Following conversion to fluorouracil, its antifungal effects are mediated through inhibition of both DNA and protein synthesis.[9] As seen in tumor cells and bacteria, fluorouracil is reduced to 5-fluorodeoxyuridine monophosphate by uracil phosphoribosyltransferase (UPRT). 5-Fluorodeoxyuridine monophosphate antagonizes thymidylate synthetase, directly inhibiting the formation of thymidylate.[10] This thymidylate deficiency results in imbalances in the nucleotide pool, impairing DNA replication and repair.

The second metabolic pathway occurs after fluorouracil has been converted to fluorouridine monophosphate by UPRT. Phosphorylation to fluorouridine triphosphate subsequently displaces up to 50% of the uridylic acid in fungal RNA.[7] Incorporation of fluorouridine triphosphate alters the aminoacylation of transfer RNA, disrupting the amino acid pool and inhibiting protein synthesis.[9,11] There exists some debate regarding the significance of either of these two different pathways to the total antifungal activity of flucytosine. Both pathways have been correlated with the degree of flucytosine susceptibility in susceptible *Candida albicans*.[9]

ANTIMICROBIAL ACTIVITY

The antifungal activity of 5-flucytosine was first described by Malbica and colleagues in 1962, with subsequent demonstration of activity in mouse models of invasive candidiasis and *Cryptococcus neoformans* fungemia.[3,4] While those initial studies noted a lack of activity against several dimorphic fungi, later studies would confirm flucytosine's narrow spectrum of antifungal activity as being primarily restricted to pathogenic yeast.

When attempting to understand the epidemiologic trends of resistance to flucytosine, it is important to note the changing definitions of antifungal susceptibility testing for flucytosine. Originally, the British Society for Medical Mycology had proposed breakpoints for interpreting fungal susceptibility to flucytosine, settling upon a minimal inhibitory concentration (MIC) of ≤1 mg/L as sensitive.[12] Similarly, the Clinical and Laboratory Standards Institute (CLSI) had previously defined clinical breakpoints for flucytosine against *Candida* species (sensitive, <4.0 mg/L; intermediate, 8.0–16.0 mg/L; resistant, ≥32 mg/L) based upon historical data and animal studies. In 2017 the CLSI removed the breakpoints, noting that insufficient data exist to set breakpoints or epidemiologic cutoff values.[13] The European Committee for Antimicrobial Susceptibility Testing (EUCAST) has not set interpretive breakpoints for flucytosine for *Candida* species. Despite the lack of clinical breakpoints or epidemiologic cutoff values, investigators have proposed pharmacokinetic/pharmacodynamic breakpoints for disseminated candidiasis. Utilizing a murine pharmacodynamic model of disseminated candidiasis paired with human population pharmacokinetics and Monte Carlo simulation, Hope and colleagues determined that a dosing regimen of 100 mg/kg/day in four divided doses resulted in a resistance breakpoint of 32 mg/L. When compared to the MIC distributions of over 1900 clinical isolates of *C. albicans*, the findings suggested that lower doses may be sufficient to treat disseminated candidiasis due to isolates with lower MICs.[14] While helpful, one cannot forget that pharmacokinetic/pharmacodynamic breakpoints are specific to both the pathogen and the disease state being studied. It is difficult to extrapolate the results obtained from the murine model of disseminated candidiasis to another clinically relevant disease state such as cryptococcal meningitis.

Among the pathogenic yeast, most *Candida* spp. are considered susceptible, with low MICs well within clinically achievable concentrations.[15] The exceptions are *Candida krusei,* in which the MICs are severalfold higher, or *Candida tropicalis,* for which high rates of primary resistance have been published.[16,17] *Cryptococcus* species are considered susceptible, although, like *C. krusei,* the distribution of MICs tends to be higher than in most *Candida* species. An analysis of several thousand multinational isolates of *C. neoformans* and *Cryptococcus gattii* species revealed a minimal inhibitory concentration for 50% of isolates (MIC_{50}) ranging from 1 to 4 μg/mL.[18]

Flucytosine is of little clinical utility against most pathogenic molds. Initial studies of flucytosine against species of *Aspergillus* noted little to no antifungal activity, but subsequent studies have found MIC values within clinically achievable concentrations of flucytosine.[19–22] Specifically, the most recent report of antifungal activity against *Aspergillus* species found a MIC_{50} for *Aspergillus fumigatus* ranging from 8 to 16 μg/mL, while the reported MIC_{50} for both *Aspergillus flavus* and *Aspergillus terreus* was ≤2 μg/mL.[22] Interestingly, the susceptibility of *A. fumigatus* to flucytosine is pH dependent. A lower pH corresponds to lower MIC values, which may indicate enhanced antifungal activity in the acidic environment of abscesses.[23] Current clinical practice guidelines do not recommend the use of flucytosine for the treatment of aspergillosis.[24] Flucytosine's activity against other filamentous fungi is mixed. Against *Mucorales, Fusarium* species, and multiple dermatophytes, flucytosine is of no clinical utility.[25,26] Conversely, flucytosine remains active against phaeohyphomycosis and chromoblastomycosis.[27]

Flucytosine is largely inactive against the dimorphic fungi. Microbiologic studies revealed little to no activity against *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides* species, *Paracoccidioides brasiliensis,* and *Sporothrix schenckii.*[4,28–30] The only dimorphic fungi for which flucytosine maintains activity is *Talaromyces marneffei.*[31]

RESISTANCE

Development of resistance has been a significant limiting factor in the utility of flucytosine as monotherapy for fungal infections. Of 23 cryptococcal meningitis patients treated with flucytosine alone, 6 of the 12 patients who failed therapy had developed resistance to flucytosine.[32] Polak and Scholer were able to establish that the resistance frequency in sensitive *C. albicans* isolates was sufficiently high to be of concern in infections with a high inoculum.[7] Specifically, the frequencies of resistant isolates of *C. albicans* when grown in 64 μg/mL of 5-fluorouracil for 7 and 14 days were 5.84×10^{-8} and 2.24×10^{-7}, respectively. This work and numerous reports of the development of resistance during therapy remain of concern.

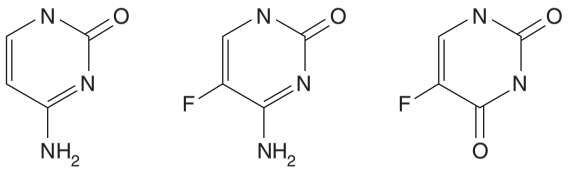

FIG. 40D.1 Comparative chemical structures of pyrimidine analogues.

As early as 1969, Grenson[33] and Jund and Lacroute[34] had described four likely mechanisms of resistance through chemical and ultraviolet mutagenesis studies of *Saccharomyces cerevisiae.* Their studies identified that resistance in *Saccharomyces* could arise from mutations affecting cytosine permease, cytosine deaminase, and UPRT activity, and from mutations giving rise to increased de novo synthesis of pyrimidines. While revealing, later studies have identified that primary resistance to flucytosine among *Candida* species is primarily mediated via decreased activity of either cytosine deaminase or UPRT.[7,35,36] Several researchers have clearly identified a single point mutation in the *FUR1* gene encoding for UPRT as accounting for most of the resistance in isolates of *C. albicans.*[37,38] Specifically, Hope and colleagues were able to demonstrate that the substitution of thymine for cytosine at position 301 of the *FUR1* gene results in a change of arginine to cysteine at amino acid 101 of the UPRTase protein. This amino acid change compromises the enzyme activity as a consequence of alterations of the quaternary structure of the enzyme.[38] Hope and colleagues were also able to describe a homozygous polymorphism in the *FCA1* gene that resulted in a glycine-to-aspartate substitution at position 28 in cytosine deaminase for a single clinical isolate of *C. albicans* resistant to flucytosine.[38] Such an understanding of the molecular mechanisms of resistance has not yet been described for *Cryptococcus* species. Recent studies have suggested that cryptococcal resistance to flucytosine is likely due to changes in an unknown protein or pathway related to regulation of flucytosine metabolism.[39–41]

PHARMACOKINETICS

Flucytosine has excellent bioavailability following oral administration. In healthy volunteers, peak serum concentrations between 30 and 40 μg/mL are seen within 2 hours of a dose of 2 g.[42,43] Similar concentrations are seen in patients with cryptococcal meningitis.[44] Absorption is delayed when following a meal or with concomitant aluminum hydroxide.[45] Overall, 78% to 89% of an oral dose is absorbed by healthy volunteers, but this is reduced in patients with renal failure and late-stage human immunodeficiency virus infection, with bioavailability estimated to be 40% to 76% and 45%, respectively.[45,46]

As a small, hydrophilic drug with minimal protein binding, flucytosine readily distributes throughout the body with a volume of distribution reflective of total body water. Regardless of kidney function, volume of distribution is estimated to be roughly 0.6 L/kg.[42,43,45,47] Protein binding of flucytosine is minimal. Regardless of concentration, studies showed that less than 4% of flucytosine was bound to protein by modified ultrafiltration, and clearance via hemodialysis was nearly indistinguishable from creatinine, corroborating the in vitro findings.[47,48] Flucytosine penetrates well into tissues, including cerebrospinal fluid, peritoneal fluid, bronchial secretions, and articular fluid.[49,50] Single-point estimates of penetration into the cerebrospinal fluid have found concentrations ranging from 60% to 90% that of corresponding serum concentrations.[44,51–53] Peritoneal fluid concentrations have ranged from as low as 5% to nearly 50% of serum concentrations and appear to be increased in the presence of inflammation.[54,55]

In mammals, flucytosine does not undergo traditional routes of metabolism. In rats, fluorouracil and its metabolites were found following oral but not intraperitoneal administration, suggesting that some oral flucytosine is deaminated by intestinal bacterial flora to fluorouracil.[56] In humans, Diasio and colleagues clearly demonstrated that while only 4% of an oral dose of flucytosine was deaminated to fluorouracil, patients

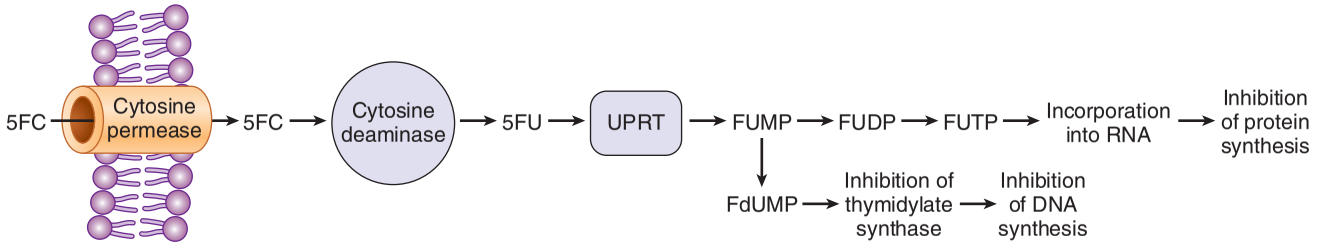

FIG. 40D.2 Mechanism of action of flucytosine. *5FC,* 5-Fluorocytosine; *FdUMP,* 5-fluorodeoxyuridine monophosphate; *5FU,* 5-fluorouracil; *FUDP,* fluorouridine diphosphate; *FUMP,* fluorouridine monophosphate; *FUTP,* fluorouridine triphosphate; *UPRT,* uracil phosphoribosyltransferase.

were exposed to concentrations previously seen with intravenous administration of fluorouracil. Several of the patients in their study developed gastrointestinal and hematologic toxicities associated with these exposures.[57] Finally, Malet-Martino and colleagues correlated the level of intestinal gram-negative bacilli with the appearance or urinary fluorouracil metabolites using fluorine-19 magnetic resonance spectroscopy.[58]

Flucytosine is predominantly eliminated unchanged by the kidneys. Evidence suggests that flucytosine is eliminated via filtration at the glomerulus with little to no tubular reabsorption or secretion.[45,47] In patients with normal kidney function, up to 95% of the dose of flucytosine is recovered unchanged in the urine within the first 24 hours.[43,45,47,56]

PHARMACODYNAMICS

Despite several decades of clinical use, the pharmacodynamics of flucytosine were not elucidated until the turn of the century. In vitro time-kill studies and in vivo mouse models confirmed the fungistatic activity of flucytosine.[59,60] Those same studies demonstrated a significant post-antifungal effect ranging from 2 to 4 hours in the in vitro studies and extended from 3.3 to 15.1 hours in the in vivo murine mouse models. In the in vitro studies, the post-antifungal effect appeared to increase with concentrations up to four times above the MIC for species of *Candida* and *Cryptococcus neoformans*.[60] Given these attributes, Andes and van Ogtrop demonstrated in a neutropenic murine mouse model of disseminated candidiasis that the pharmacokinetic/pharmacodynamic parameter most predictive of microbiologic effect was the time above the minimum inhibitory concentration (T>MIC). Specifically, serum concentrations need only exceeded the MIC for 20% to 25% of the dosing interval for maximal microbiologic effect.[59]

Due to evidence of the rapid induction of resistance, flucytosine has been used almost entirely in combination with a second antifungal. Initial studies suggested combinations of amphotericin B and flucytosine exhibited synergistic fungicidal activity against *C. albicans, C. tropicalis,* and *C. neoformans*.[61] Subsequent animal model studies confirmed the synergistic nature of this combination against *Candida* spp.[62,63] Hope and colleagues further elucidated the additive effects of this interaction in a well-validated pharmacodynamic animal model of invasive candidiasis.[64] In the treatment of cryptococcal meningitis, the combination of fluconazole and flucytosine reduced the dose of flucytosine required for an antifungal effect and abrogated the need for higher doses of fluconazole with increased severity of meningitis.[65,66]

DOSING, ADMINISTRATION, AND MONITORING

In the United States, flucytosine is only available as oral capsules of 250 and 500 mg.[67] Elsewhere, an intravenous formulation is also available.[68] The usual dose in patients with normal renal function for both intravenous and oral administration is 25 to 37.5 mg/kg every 6 hours (100–150 mg/day).[67] The recommendation is similar for pediatric patients, although this dosing regimen tends to result in slightly higher concentrations in neonates. Pharmacokinetic studies have clearly demonstrated that the clearance of flucytosine is almost completely reflective of the glomerular filtration rate, allowing simplified dosing nomograms to be proposed by multiple investigators.[43,47,69,70] Considering the degree of variability in these dosing recommendations, determining the appropriateness of a regimen to ensure clinical efficacy and minimize toxicity is relevant. Ette and colleagues evaluated two different dosing strategies in hospitalized adults utilizing a population pharmacokinetic approach and determined that a dosing regimen starting at 150 mg/kg/day resulted in more concentrations outside the desired therapeutic range and had less convenient dosing intervals.[71] Furthermore, Hope and colleagues evaluated the most appropriate dosing strategy for flucytosine in combination with amphotericin B for the treatment of disseminated candidiasis utilizing a pharmacokinetic/pharmacodynamic approach and found that significantly lower doses of flucytosine (25 mg/kg/day) were able to achieve the target time above the MIC for all isolates with a MIC of less than or equal to 1 μg/mL.[72] These findings suggest the value of pairing individual microbiologic data with pharmacokinetic/pharmacodynamic modeling to allow dosing regimens that minimized toxicity while maintaining optimal microbiologic efficacy.

Therapeutic Drug Monitoring

Early in the study of flucytosine, it became evident that associations between the development of resistance, toxicities of flucytosine, and serum concentrations existed.[35,70] Additionally, decades of experience monitoring serum concentrations of flucytosine have demonstrated that despite a well-delineated pharmacokinetic profile, there remains significant variability in predicted exposures.[73,74] The combination of the association of clinically relevant serum concentrations with microbiologic outcomes and toxicity and the variability in predicted pharmacokinetics make flucytosine an ideal candidate for therapeutic drug monitoring.

The development of resistance through flucytosine therapy was noted early in treatment of pathogenic yeast employing monotherapy.[32,52,75] By exposing *Candida* spp. to progressively increasing concentrations of flucytosine in an effort to select for resistant strains, Normark and Schönebeck noted that the number of resistant mutants was considerably higher in concentrations less than 25 μg/mL.[35] Based upon this observation, they postulated that in vivo concentrations should not be below this concentration. Nearly 30 years would pass before a new understanding of pharmacokinetic/pharmacodynamic relationships would elucidate more well-defined targets for optimizing the efficacy of flucytosine.[59,60] Specifically, targeting concentrations to exceed the MIC of the isolate for at least 20% to 25% of the dosing interval is optimal for disseminated candidiasis.[59] Similar targets have not been defined for cryptococcal disease.

Similarly, an association between elevated concentrations and significant toxicities appeared rather apparent in early clinical experience.[76,77] Multiple investigators have established the association between concentrations greater than 100 μg/mL for periods of 2 or more weeks and the development of myelosuppression and, perhaps, hepatotoxicity.[70,78] Following observations of the detection of 5-fluorouracil and its catabolites in urine and serum of patients receiving oral flucytosine, early studies had suggested that conversion of flucytosine to 5-fluorouracil by gastrointestinal bacteria was responsible for these observed toxicities.[57,58,79,80] While this apparent relationship may describe much of the toxicodynamics of flucytosine, no studies have described an association between 5-fluorouracil concentrations and the toxicities associated with flucytosine.[70,81] Thus from a toxicity perspective, routine monitoring of flucytosine concentrations is of the most utility clinically.

These inherent aspects of flucytosine therapy have resulted in routine monitoring of flucytosine concentrations throughout its clinical history. The British Society for Antimicrobial Chemotherapy Working Party first published guidelines for the therapeutic drug monitoring of antifungals, noting that serum concentrations of flucytosine were useful in all patients, and essential with renal impairment or when used in combination with amphotericin B.[82] Dosing was recommended to maintain peak concentrations of 70 to 80 mg/L and trough concentrations of 30 to 40 mg/L. More recent preclinical infection models have established that serum concentrations need not exceed the MIC for more than 50% of the dosing interval and that little to no benefit is gained from increasing concentrations markedly above the MIC.[14,59] While these findings are promising regarding their implications for dosing strategies that may optimize efficacy and minimize toxicity, there are as of yet no clinical trials evaluating these targets in the disease states of interest. Thus even recent guidelines for the therapeutic drug monitoring of antifungals has continued to recommend trough concentrations of >20 to 40 mg/L and peak concentrations of 50 to 100 mg/L for optimal antifungal activity and to minimize toxicity, respectively.[83]

TOXICITY

As one of the oldest antifungals available for clinical use, flucytosine has a toxicity profile that is rather well understood. Oral flucytosine monotherapy is relatively well tolerated, with most adverse reactions occurring in fewer than 10% of cases.[84] Despite this, over 30% of patients receiving amphotericin B and flucytosine develop one or more toxicities to flucytosine in most trials; this usually occurs in patients with amphotericin B–induced azotemia. The most well-established toxicities include gastrointestinal toxicities, hepatotoxicity, and myelosuppression. While much of the toxicity attributed to flucytosine appears to be largely concentration dependent, concurrent nephrotoxicity is associated with

concomitant amphotericin B. Changes in gastrointestinal flora might also play a contributing role.[85]

Gastrointestinal

One of the most common toxicities of oral flucytosine, gastrointestinal complaints occur in up to 18% of patients and manifest primarily as nausea and diarrhea.[70] Most cases occur during the first week or two of therapy and persist for only a few days before resolving spontaneously or with dose reductions. More severe cases may also develop anorexia, vomiting, profuse diarrhea, and mild diffuse abdominal pain.[84] Rarely, colonic perforation or colitis has led to a fatal outcome.[32,84]

Myelosuppression

Some degree of myelosuppression occurs in roughly 20% to 30% of patients.[53,70,86,87] It primarily manifests as neutropenia or thrombocytopenia. In the setting of neutropenia, bone marrow biopsy demonstrates hypocellularity with decreased granulocyte lineage.[88] Onset is typically within the first 2 to 3 weeks of therapy and has been associated with prolonged exposure to concentrations above 100 μg/mL.[70,78] Notably, Stamm and colleagues found that neutropenia or thrombocytopenia occurred in 12 (60%) of 20 patients with flucytosine concentrations greater than 100 mg/L, and in only 8 (12%) of 65 patients with flucytosine concentrations less than 100 mg/L.[70] Deaths have occurred from leukopenia and from thrombocytopenia,[84] but near-complete resolution occurs within 1 to 2 weeks with discontinuation or dosage reductions.

Hepatotoxicity

Hepatotoxicity is another common adverse reaction associated with flucytosine therapy. Estimates of the incidence of hepatotoxicity vary from as low as 7% to as high as 41%.[70,84,86,87] The significant variation in the estimated incidence of hepatotoxicity may only be reflective of the criteria used to define hepatotoxicity, with more strict criteria reflecting the highest estimates. Flucytosine hepatotoxicity primarily manifests as a transient, mild-to-moderate transaminitis with accompanying elevated alkaline phosphatase.[89] Elevations in bilirubin are uncommon and instances of acute liver injury and hepatic failure appear to be extremely rare. While the exact mechanism has not been fully elucidated, evidence does suggest that it is not dose dependent, with resolution occurring upon discontinuation.[70]

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41 Antimalarial Drugs

James S. McCarthy and Richard N. Price

SHORT VIEW SUMMARY

- The pharmacology of the major drugs is discussed in this chapter. For details of diagnosis and drug doses, the reader is referred to Chapter 274, with treatment summarized in Table 274.3 and prophylaxis in Table 274.4 of that chapter.
- Drugs in the artemisinin class are the first-line treatment of choice for all malaria species because of their rapid action, safety, and activity against all species. They can be given by oral, intravenous (IV), intramuscular (IM), or intrarectal route. They are generally coadministered with partner drugs, such as lumefantrine (Coartem in the United States), amodiaquine, piperaquine, pyronaridine, or mefloquine, so-called artemisinin combination therapy (ACT). The pharmacology of these partner drugs is discussed in this chapter.
- Reduced artemisinin susceptibility has been documented in Cambodia and other countries in the Greater Mekong Region.
- Uncomplicated malaria can also be treated with one of the following: atovaquone-proguanil (Malarone), mefloquine, or quinine plus either doxycycline, tetracycline, or clindamycin.
- Complicated malaria should be treated with IV artesunate (available through the Centers for Disease Control and Prevention), quinidine, or quinine (IV quinine is not available in the United States).
- Options for prophylaxis against chloroquine-resistant falciparum malaria include once-weekly mefloquine, once-daily doxycycline, or once-daily atovaquone-proguanil. Mefloquine use is limited by central nervous system side effects. Doxycycline photosensitivity and cost of atovaquone-proguanil are considerations.
- Primaquine can be used for prophylaxis during travel or used after return from malarious areas to lessen incidence of recurrent vivax malaria. Travelers should be tested for glucose-6-phosphate dehydrogenase deficiency before use. Tafenoquine is a new long-acting drug that is now approved by the US Food and Drug Administration and can be used as a substitute for primaquine.
- The pharmacology of sulfadoxine and pyrimethamine is included in this chapter.

Antimalarial drugs can be classified in the following ways: chemical class, mechanism of action, or life-cycle stage of the parasite against which they are active. In clinical medicine the priority of antimalarial chemotherapy is to clear the blood-stage infection that causes illness and prevent disease progression to severe malaria and death. Although all antimalarials are active against the asexual blood stages, a few also have activity against the preerythrocytic life-cycle stage in the blood (sporozoites) and liver. Such activity makes these drugs useful for chemoprophylaxis and for the elimination of latent infection with hypnozoites of *Plasmodium vivax* and *Plasmodium ovale*. Drugs with activity against gametocytes, the sexual stages of the parasite, have potential to reduce the ongoing transmission of the parasite to the mosquito; this has important public health benefits in areas where *Anopheles* vectors are present. The life-cycle stages targeted by available antimalarial drugs are shown in Fig. 41.1.

Pharmacokinetic properties of major antimalarials are presented in Table 41.1 and discussed with each drug.

ARTEMISININ DERIVATIVES

Artemisinin is the active principle extract of *Artemisia annua* (Qinghao), a plant used for centuries in traditional Chinese herbal remedies for the treatment of febrile illness. In the 1960s Chinese scientists began an extensive search for new antimicrobial compounds from their traditional pharmacopoeia, a search that brought to light the novel antimalarial properties of artemisinin.[1] These compounds are unusual in that they consist of a peroxide bridge within a 1,2,4-trioxane configuration, which contains a sesquiterpene lactone ring. The endoperoxide bridge is essential for their antimalarial activity.[2] Artemisinin and its derivatives are highly potent antimalarials, with a broad-stage specificity of action, resulting in a faster clinical and parasitologic response than any other antimalarial agents in clinical use. The importance of this new antimalarial class of drugs was acknowledged in the 2015 Nobel Prize for Medicine awarded to Tu Youyou for her contribution to the discovery program.

The use of the parent compound artemisinin has been superseded by the development of four main derivatives: water-soluble hemisuccinate artesunate and its active metabolite dihydroartemisinin (DHA), and the lipophilic methyl ethers artemether and artemotil (formerly known as arteether). Artesunate, the most widely used of the derivatives, is available in oral, intravenous (IV), intramuscular (IM), and rectal formulations. It is the only member of this class that can be administered IV. Artemether, a methyl ether derivative, can be administered by IM injection suspended in oil or as capsules for oral administration. Novel synthetic and semisynthetic derivatives with potent antimalarial activity in vitro have also been developed.[3] Two synthetic trioxolanes, arterolane (OZ277) and artefenomel (OZ439), have been developed. Arterolane is marketed in a fixed-dose coformulation with piperaquine called Synriam.[4] Artefenomel is currently under development in combination with ferroquine.[5,6]

Structures of Artemisinin Compounds

The artemisinin derivatives demonstrate excellent efficacy against all human malaria parasites, including multidrug-resistant strains of *Plasmodium falciparum*[7] and *Plasmodium vivax*[8] (Fig. 41.2). These drugs have also been shown to have in vitro activity against other parasites, including *Schistosoma, Fasciola, Opisthorchis, Clonorchis,* and *Leishmania,* although susceptibility is more modest, and they have not received the same degree of preclinical and clinical development for these indications.[9–11] Although the activity of the artemisinins is known to be dependent on the endoperoxide dioxygen bridge, their exact mechanism of action remains unclear. The active endoperoxides accumulate in various parasite compartments, including the cytosol, digestive vacuole, and membranes. The interaction between the drug and intraparasitic heme-derived iron appears to be a crucial step both in vitro and in vivo,[12,13] in which the endoperoxide bridge is cleaved to hydroperoxide, the resultant hydroperoxide-metal complex acting as a powerful oxidizing agent, releasing carbon-centered free radicals and other reactive

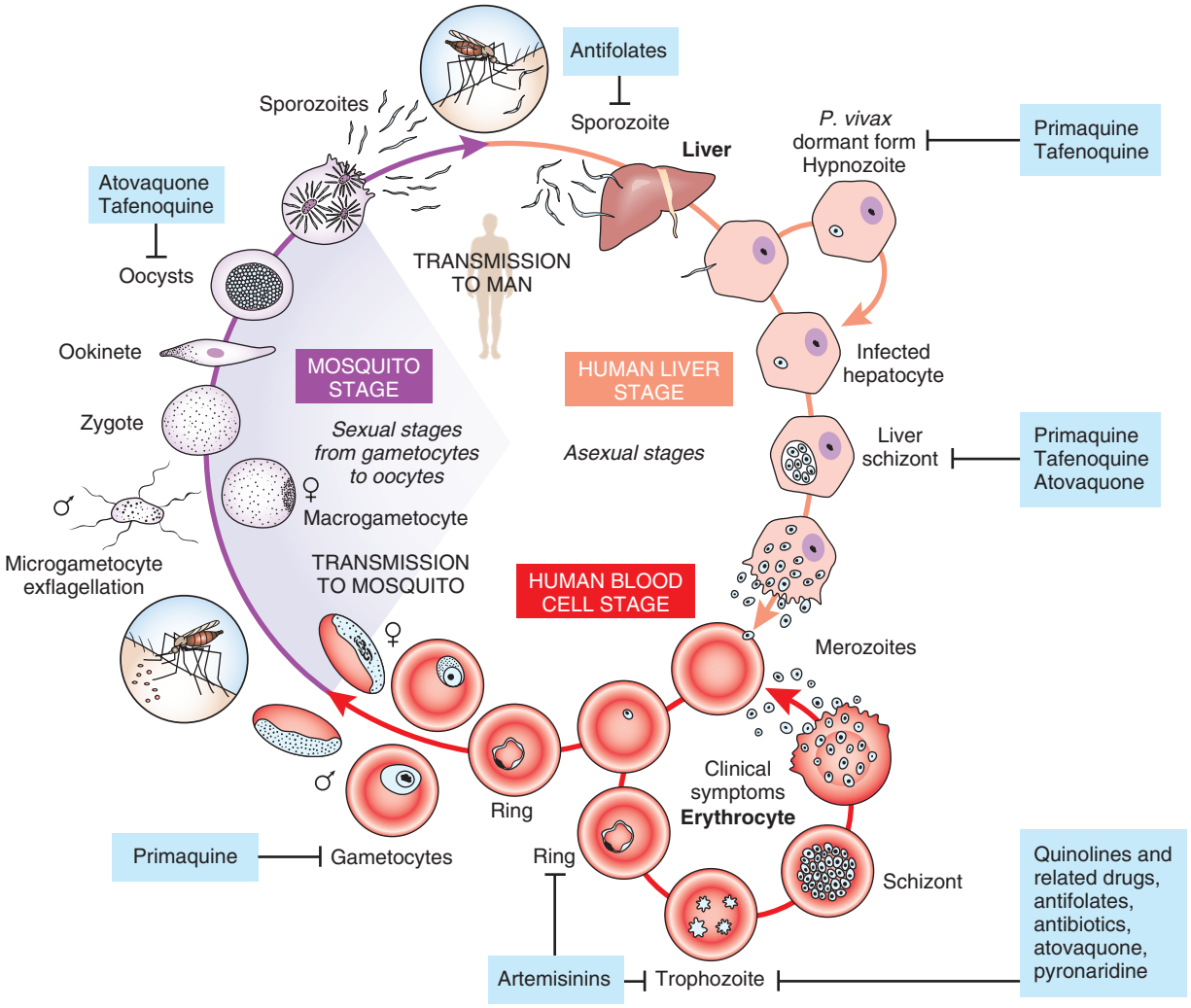

FIG. 41.1 Summary of the activity of the most widely used antimalarials throughout the life cycle of *Plasmodium*. The three main phases (i.e., liver stage, blood stage, and vector stage) of the life cycle of *Plasmodium* are shown. Parasite forms specific to each stage are highlighted, and drugs identified as inhibitors of development of these forms are listed in boxes. *(Modified from Delves M, Plouffe D, Scheurer C, et al. The activities of current antimalarial drugs on the life cycle stages of Plasmodium: a comparative study with human and rodent parasites.* PLoS Med. *2012;9: e1001169.)*

metabolites.[14,15] These reactive metabolites bind with hemin, parasite proteins, and red cell membranes, which are thought to cause critical damage to parasite organelles.[16] Other studies have implicated interference with calcium homeostasis, a translationally controlled tumor protein (TCTP) homologue, the mitochondrial electron transport chain, and inhibition of angiogenesis.

Pharmacokinetics and Dynamics

Bioavailability of the artemisinin compounds varies with the route of administration and duration of therapy. Artesunate is metabolized almost immediately to DHA and therefore can be considered a prodrug; pharmacokinetic studies therefore tend to present the profile of DHA rather than the parent compound. Peak plasma concentrations (C_{max}) of DHA occur at 10 minutes after IV injection of artesunate, 30 to 40 minutes after IM injection, and 1 to 2 hours after oral and rectal administration.[17,18] The bioavailability of oral artesunate is approximately 60%[17,19] but falls to 16% when administered rectally,[18] whereas the bioavailability of DHA after artesunate is 86% to 88% when it is given parenterally.[20] The bioavailability of artemisinin after oral administration is significantly less (32%) and is far more variable than that for oral artesunate,[21] ranging from 43% to 200%.[22,23] Bioavailability of artemether when administered by IM injection is variable; C_{max} vary between 2 and 10 hours after injection.[24]

Host factors can affect the bioavailability of some artemisinin derivatives. The bioavailability of DHA is increased twofold in patients with malaria, compared with healthy volunteers,[25] and is twofold higher during the acute phase of infection compared with convalescence.[19] However, in pregnant women with malaria the bioavailability of artesunate is reduced fourfold compared with nonpregnant malaria patients.[26] The bioavailability of oral artemisinin, but not artesunate, falls by more than 80% after 5 days of treatment, a process thought to relate to autoinduction of metabolism.[27]

Once artemether and artesunate are absorbed, there is extensive first-pass metabolism and rapid biotransformation to DHA. The elimination half-life of DHA is less than 1 hour.[18,20] The elimination half-life of artemether and DHA after artemether, given either orally or intramuscularly, is longer, varying from 2 to 12 hours. Metabolic pathways for the biotransformation of artesunate, artemether, and DHA differ from that observed for the parent compound artemisinin. Artemether is metabolized predominantly by the hepatic cytochrome CYP3A4 to DHA. DHA is metabolized by hepatic cytochrome P-450, involving biotransformation to biologically inert glucuronides that are eliminated in bile.[28]

DHA blood concentrations are reduced after IM and IV administration of artesunate in children weighing between 6 and 10 kg compared with older children and adults, and thus a higher dose is recommended