Systemic antifungal agents and their use for the therapy of invasive mycoses are discussed in this chapter. Many of these agents can also be used to treat the mucocutaneous forms of candidiasis, but those uses are discussed in detail in Chapter 257 and thus are mentioned only in passing here. Similarly, the therapy of the various forms of tinea and onychomycosis with topical agents or systemic agents is discussed in Chapter 267. Although Pneumocystis jirovecii (formerly Pneumocystis carinii) is now classified with the fungi, the drugs used to treat it are principally used to treat parasitic infections. Those drugs and their uses are discussed in Chapters 44 and 270.

**Amphotericin B–Based Preparations**

**GENERAL FEATURES**

**Mechanism of Action**
Amphotericin B is available in a formulation with deoxycholate and in three lipid-associated formulations. For all preparations, the active component is amphotericin B produced by Streptomyces nodosus. Amphotericin B is a lipophilic molecule (Fig. 40-1) 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 (Fig. 40-2). At lower drug concentrations, 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. Amphotericin B also has effects via oxidative pathways that may enhance antifungal activity. The possible effects of amphotericin B and its lipid formulations on the immune system have been recently reviewed.3

**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.4 Resistance may also follow from increased production of reactive oxidant scavengers.5 Primary resistance is common for Aspergillus terreus, Scedosporium species, and Trichosporon species.4 Among the Candida species, primary resistance is noted infrequently, most often for Candida lusitaniae. Development of resistance in isolates of normally susceptible species is uncommon, but has been described for essentially all common pathogens. Although such isolates may exhibit altered growth and reduced pathogenicity,5 invasive and lethal infections are well described. Identification of amphotericin B–resistant isolates by standardized susceptibility testing methods is difficult and optimal methods are as yet undefined.5 In studies of amphotericin B deoxycholate as therapy for candidiasis, the principal pharmacodynamic driver of an in vivo response has been ratio of the peak achieved serum concentration to the minimal inhibitory concentration (MIC).6

**AVAILABLE FORMULATIONS**

There are four commercially available amphotericin B formulations. Amphotericin B deoxycholate (ABD; Fungizone) was licensed in 1959 in the United States.9 More recently, three lipid-associated formulations have been marketed: amphotericin B colloidal dispersion (ABCD; Amphotec, Amphocil), amphotericin B lipid complex (ABLC; Abelcet), and liposomal amphotericin B (LAMB; AmBisome).9 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 dosage of 1 mg/kg daily than with infusions of ABD in 5% dextrose,10 no advantage was found in children11 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 the 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 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, the colloidal nature of ABD is easy to demonstrate. If a filter with a 0.22-μm pore diameter is placed in the infusion line, considerable drug is removed by the filter. The addition of electrolyte will aggregate the colloids, so the solution becomes cloudy when saline or sodium bicarbonate is added to an ABD solution. 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 this compound.9

**Pharmacology.** Concentrations of amphotericin B in biologic fluids have usually been measured by bioassay, but high-pressure liquid chromatography,12 immunoassay,13 and radiometric respirometry14 have been described. Despite the proliferation of methods, routine determination of amphotericin B serum, urine, or cerebrospinal fluid 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 amphoteri-
cin B in fluid from inflamed areas, such as pleura, peritoneum, joint, 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 cerebrospinal fluid (CSF, whether meninges are normal or inflamed), saliva, bronchial secretions, brain, pancreas, muscle, bone, vitreous humor, or normal amniotic fluid. Urine concentrations are similar to serum concentrations. Peak serum concentrations with conventional intravenous doses are roughly 0.5 to 2.0 µg/mL and rapidly fall initially to approach a plateau slowly of roughly 0.2 to 0.5 µg/mL.14 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. The drug also has complex immunomodulatory properties, potentially of clinical significance but presently undefined.

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.15 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 caused by destruction of renal tubular cells, disruption of tubular basement membrane, and loss of functioning nephron units. Saline loading, such as infusion of 1 L of saline before ABD, has been associated with reduced nephrotoxicity in some studies but not

Figure 40-1 Structures of the systemic antifungal agents.
Potassium wasting often requires 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.

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 (see later).

Early in a course of therapy with ABD, azotemia may increase rapidly, often falls slightly, 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.

**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

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**Figure 40-1, cont’d**

**Figure 40-2**  Mechanisms of action of the antifungal agents. Shown are the major mechanisms and sites of action for currently licensed antifungal agents. Many of the precise details of the physical interactions are not known and the diagram is at best an approximation. The interaction between amphotericin B (A) and ergosterol (E) in the fungal cell membrane is consistent with the formation of pores with a diameter of approximately 0.8 nm. The structure of the pore is not known, but available data suggest that amphotericin molecules would line the inner surface of the pore. These pores permit leakage of intracellular contents. The interaction between the echinocandins and glucan synthase leads to reduced synthesis of (1→3)-β-D-glucan, a critical component of the interwoven glucan polymers that form the fungal cell wall. The site of action of the echinocandin and molecular mechanism of the inhibition are, however, unsettled. The azole antifungal agents act within the cell to inhibit 14α-demethylase and thus reduce the synthesis of ergosterol, a sterol critical to cell membrane stability. Flucytosine is converted into 5-fluorouridine triphosphate (5FUTP) and incorporated into fungal RNA, thus becoming an inhibitor of fungal protein synthesis, or is converted into 5-fluorodeoxyuridine monophosphate (5FdUMP), an inhibitor of thymidylate synthetase and thus of DNA synthesis. These compounds presumably are created in the cytoplasm, with subsequent diffusion into the nucleus. 5-FC, 5-fluorocytosine; 5-FU, 5-fluorouracil.
plasma erythropoietin levels than anticipated from the level of anemia. This hematocrit rarely falls below 20% to 25% unless other causes of anemia are present. Rarely, thrombocytopenia, modest leukopenia, arrhythmias, coagulopathy, hemorrhagic enteritis, incontinence, encephalopathy, seizures, hemolysis, 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 type 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.

**Administration.** ABD is infused in 5% dextrose over a 2- to 4-hour infusion interval. An infusion of 1 hour in duration appears to generally be safe for persons who have tolerated slower infusions and may be advantageous for outpatient therapy. Early in the course of therapy, fever is more pronounced with infusion intervals of only 45 minutes than infusion lasting 4 hours. Rapid infusion in patients with severely compromised renal function may lead to acute marked hyperkalemia and ventricular fibrillation. Once therapy is well under way, patients receiving a stable daily dose may be changed to a double dose on alternate days to reduce the frequency of infusion-associated toxicity, particularly anorexia, and as a consequence for outpatient therapy. Doses above 1.5 mg/kg are not generally given on this schedule because the toxicity of such infusions is not well described. Amphotericin B should not be switched to alternate-day administration at the same dosage as daily therapy; this results in reduced trough serum concentrations and may lead to serious underdosing. Continuous infusion of amphotericin B with doses up to 2.0 mg/kg/24 hr has been described based on limited data as another approach to reduction of toxicity, but this approach is not consistent with the observation that the principal pharmacodynamic driver of efficacy for amphotericin B is peak drug concentration.

**Dosage.** Daily ABD dosages of 0.3 mg/kg often suffice for esophageal candidiasis. A dose of 0.5 mg/kg is appropriate for blastomycosis, disseminated histoplasmosis, and cutaneous sporotrichosis. Patients with cryptococcal meningitis are generally given 0.6 to 0.8 mg/kg; those with coccidioidomycosis may require 1 mg/kg. Patients with zygomycosis or invasive aspergillosis are given daily dosages 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 309). Local instillation of amphotericin B into cerebrospinal fluid, joints, or pleura is rarely indicated. One exception is coccidioidal meningitis, which is 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 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 may be obtained with oral fluconazole.

**Lipid-Associated Formulations of Amphotericin B**

**General.** The three lipid-associated formulations of amphotericin B are licensed in the United States for a variety of indications and at a range of doses. When using these agents, it is critical to be aware of the ease with which their names can be confused. Only one of the products (LAMB) is a liposomal formulation. The other two, ABLC and ABCD, are aggregates of lipid and amphotericin B rather than liposomes. The problem is that the phrase “liposomal amphotericin B” is often used mistakenly as a label for the entire class of compounds. Thus, this chapter uses lipid-associated formulation of amphotericin B (LABF) as a general label for the class. Because the tolerance to one product does not always translate into tolerance for another, it is important that the physician use an unambiguous name when prescribing these compounds.

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). LABM is licensed for empirical therapy for presumed fungal infection in febrile neutropenic patients (3 mg/kg/day); treatment of cryptococcal meningitis in HIV-infected patients (6 mg/kg/day); treatment of patients with *Aspergillus*, *Candida*, and/or *Cryptococcus* infections refractory to amphotericin B deoxycholate or patients for whom renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate; and treatment of visceral leishmaniasis (3 to 4 mg/kg/day). ABCD is licensed for treatment of invasive aspergillosis in patients for whom renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate and treatment of visceral leishmaniasis (3 to 4 mg/kg/day). ABCD is licensed for treatment of invasive fungal infections in patients who have tolerated slower infusions and may be advantageous for outpatient therapy.

**Pharmacology and Toxicity.** The three LAFBs have different pharmacokinetic patterns. When compared on the basis of equal mg/kg dosages, LAFBs produce tissue amphotericin B concentrations that range from 90% lower to 500% higher than those seen for ABD, with the most consistent relative reduction seen in the kidney (80% to 90% reduction). Because LAFBs are typically given at mg/kg doses that are 6- to 12-fold higher than those used for ABD, the relevance of these comparisons is uncertain, although it is generally clear that all three LAFBs require higher doses in experimental animals to achieve the same therapeutic effect as ABD.

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

**Amphotericin B Colloidal Dispersion.** ABCD, which contains cholesterol sulfate in equimolar amounts to amphotericin B, forms disk-like colloidal particles about 122 ± 48 nm in diameter. Like ABD, it forms a clear yellow solution when hydrated. A randomized, prospective, double-blind comparison of ABD, 0.8 mg/kg/day, and ABCD, 4 mg/kg/day, was done in neutropenic patients whose fever had not abated after 72 hours of antibacterial therapy. Efficacy was the same in the 98 patients receiving ABCD as in the 95 receiving ABD, with 53% and 58%, respectively, becoming afebrile after 48 hours and 14% and 15% as compared with 15% having a suspected or documented mycosis emerge during amphotericin B therapy. Acute febrile reactions were significantly more common with ABCD than ABD, with hypoxia developing in 15% and 3%, respectively. The percentage of patients having amphotericin B therapy discontinued because of some toxicity was the same in the two arms (14% and 15%), with the ABD discontinuations much more often being caused by azotemia. In a randomized double-blind study of ABCD (6 mg/kg/day) versus ABD (1 to 1.5 mg/kg/day) as therapy for invasive aspergillosis, response rates for the two therapies were
similar (52% vs. 51%, respectively) with reduced rates of nephrotoxicity noted with ABCD (25% vs. 49%). However, infusion-related chills and fever were more common with ABCD than with ABD. The recommended dose for adults and children is 3 to 4 mg/kg once daily infused as 0.6 mg/mL at a rate of 1 mg/kg/hr. The infusion can be increased to a duration of 2 hours for patients who tolerate the drug well. Premedication with acetaminophen has not been studied prospectively but should be considered.

**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 of 556 adult and pediatric patients and of 111 pediatric patients. All patients in these studies had either failed prior ABD therapy or were intolerant of ABD therapy. Of the enrolled patients, only 343 were considered to have a documented mycosis and had sufficient data to evaluate the drug’s therapeutic effect. If all the mycoses are considered together, a complete response to ABLC was judged to have occurred in 28% and a partial response in 32%, for an overall response rate of 60%.

**Liposomal Amphotericin B.** LAMB is 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 hydroxylated soy lecithin—cholesterol—disteroyl phosphatidylglycerol 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. A randomized three-way comparison of LAMB at 3 mg/kg/day, LAMB at 6 mg/kg/day, and ABD at 0.7 mg/kg/day for cryptococcal meningitis enrolled 267 HIV-infected subjects and reported global response rates of 66%, 75%, and 66% respectively. A randomized comparison of LAMB at 3 mg/kg/day versus AMD at 0.7 mg/kg/day for histoplasmosis in HIV-infected subjects reported superior efficacy for LAMB (89% vs. 59% response; P < .01). Open-label efficacy data in patients with invasive mycoses (mostly candidiasis and aspergillosis) not responding to or intolerant of ABD have also been reported. Of the patients in these studies with defined mycoses and evaluable outcomes, 118 of 161 (73%) were judged to have a complete or partial response to therapy. The European Organization for Research and Treatment of Cancer conducted a prospective randomized comparison of 1 and 4 mg/kg LAMB in 120 patients with proven and probable aspergillosis. Of the 87 evaluable patients, responses were the same in the 41 receiving 1 mg/kg as in the 46 receiving 4 mg/kg, although the group receiving the higher dosage contained the greater proportion of subjects with proven (rather than probable) aspergillosis. In a subsequent study, the response rate for invasive aspergillosis after 2 weeks of therapy was the same at 3 mg/kg/day (50% of 107 patients) as at 10 mg/kg/day (46% of 94 patients) but with greater nephrotoxicity and hypokalemia at the higher dosage.

Three prospective randomized studies in adults and children have compared LAMB with ABD in neutropenic patients with fever not responsive to 96 hours of antibacterial antibiotics. The U.S. study compared 343 patients receiving 1.5 to 6.0 mg/kg LAMB daily and 344 adults receiving 0.3 to 1.2 mg/kg ABD daily. Even though some patients received relatively low doses of ABD, the two regimens had identical efficacy. A subset analysis of possible and proven mycoses emerging during therapy suggested an advantage for LAMB. A report of two combined studies in Europe that compared ABD, 1 mg/kg, with LAMB, 3 mg/kg, also found equal efficacy in neutropenic patients failing 96 hours of antibacterial therapy. No difference was noted in mycoses emerging during empirical therapy. These studies generally suggest that LAMB causes less nephrotoxicity and less severe hypokalemia than ABD, a result supported by a direct comparison of these two formulations. A 1- to 2-mg/mL infusion over a 2-hour period is recommended. Infusion intervals can be shortened to 60 minutes in patients for whom the treatment is well tolerated. A trial 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. These reactions are effectively managed by diphenhydramine administration and brief interruption of the LAMB infusion. LAMB is the only lipid-associated amphotericin B formulation that does not contraindicate the use of an in-line filter, although pore size should be at least 1.0 µm.

**Comparison of Amphotericin B Deoxycholate and 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. Randomized comparisons with ABD as therapy in the persistently neutropenic and febrile cancer patient provide consistent demonstrations of a generally better tolerability profile, but little data on differential treatment effect other than a subset analysis showing a reduced rate of breakthrough infections in one study. Consistent with these results, the aggregate open-label data efficacy rates for the LFABs are similar to those for ABD. Although LFABs are notably more costly than ABD (from 10 to 60 times more), the purchase cost of the compound must be balanced against the morbidity and financial costs of monitoring, treating, and managing ABD-related nephrotoxicity. Importantly, such toxicity may be well tolerated in an outpatient with few other comorbidities, 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%.

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 other two classes, ABLC and liposomal amphotericin B remain appropriate for acute management of severe disseminated histoplasmosis, initial management of cryptococcosis, and treatment of suspected zygomycosis. 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. Use of ABCD has been restricted by the high incidence of acute reactions and the relative paucity of efficacy data.

**Inhaled Amphotericin B**

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

[Image: Flucytosine]

**Flucytosine**

**Formulation and Pharmacology.** Flucytosine (5-fluorocytosine; Ancobon) is the fluorine analogue of a normal body constituent, cytosine (see Fig. 40-1). Flucytosine is moderately soluble in water, very stable in dry storage, and marketed as 250- and 500-mg capsules. Absorption from the gastrointestinal tract is rapid and complete, and approximately 90% is excreted unchanged in the urine. Protein binding is barely measurable. Cerebrospinal fluid concentrations approximate 74% of simultaneous serum concentrations. Limited data suggest
that it also penetrates well into aqueous humor, joints, bronchial secre-
tions, peritoneal fluid, brain, bile, and bone. The drug is readily cleared by
hemodialysis and peritoneal dialysis.

The half-life of the drug in the serum of patients with normal renal
function is 3 to 5 hours and higher in newborns. Abnormal hepatic
function has no influence, but decreased renal function prolongs the
half-life.

other than Candida krusei are usually susceptible to flucytosine, as
are most current isolates of Cryptococcus neoformans. It is often active
against isolates of Aspergillus spp. and against the melanin-pigmented
molds that cause chromoblastomycosis. The mechanism of flucyto-
sine’s antifungal action appears to be by deamination to 5-fluorouracil
and then conversion through several steps to 5-fluorodeoxyuridylic
acid monophosphate, a noncompetitive inhibitor of thymidylate synth-
ase, which interferes with DNA synthesis, or through its conver-
sion to 5-fluorouridine triphosphate, which causes aberrant
transcription (see Fig. 40-2).4 In studies of therapy of candidiasis, the
principal pharmacodynamic driver of response was the proportion of
the time the blood level exceeded the MIC.5 Resistance may be caused
by loss of the cytosine permease that permits flucytosine to cross the
fungal cell membrane or loss of any of the enzymes that lead to its
conversion into the forms that interfere with DNA or RNA synthesis.
Induction of resistance during monotherapy is sufficiently frequent
and rapid that flucytosine is essentially always used as part of combina-
tion therapy.

Administration and Dosage. Flucytosine is usually administered by
mouth at 100 to 150 mg/kg/day in four divided doses. Patients with a
serum creatinine level of 1.7 mg/dL or higher usually require dose
reduction. As an approximation, the total daily dosage should be
reduced to 75 mg/kg with a creatinine clearance of 26 to 50 mL/min
and to 37 mg/kg when the creatinine clearance is 13 to 25 mL/min.31
Ideally, the blood level should be measured in azotemic patients 2
hours after the last dose and immediately before the next dose. The
target blood level range has long been thought to be between 20 and
100 µg/mL, although recent pharmacodynamic work has suggested
that levels of 10 to 50 µg/mL would be adequate.32 Patients requiring
hemodialysis may be given a single postdialysis dose of 37.5 mg/kg.
Further doses are adjusted by blood level. Reliable biologic,49 enzy-
matic,52 and physical51 methods are available to assay flucytosine, even
in the presence of amphotericin B.

Flucytosine given alone to patients with normal renal, hematologic,
and gastrointestinal function is associated with very infrequent adverse
effects, including rash, diarrhea, and, in about 5%, hepatic dysfunc-
tion. In the presence of azotemia such as that caused by concomitant
amphotericin B, leukopenia, thrombocytopenia, and enterocolitis may
appear and can be fatal. These complications seem to be far more
frequent among patients whose flucytosine blood levels exceed 100 µg/mL and especially if they exceed 125 µg/mL.33 Patients receiv-
ing flucytosine whose renal function is changing should have their
serum flucytosine concentrations determined as often as twice weekly
and the leukocyte count, platelet count, alkaline phosphatase, and
aminotransferase levels determined at a similar frequency. Patients in
whom loose stools or dull abdominal pain suddenly develops or who
have laboratory evidence consistent with flucytosine toxicity should
have their flucytosine blood levels determined and consideration given
to withholding therapy with the drug until the situation is clarified.
Patients with bone marrow and gastrointestinal toxicity from flucyto-
sine often tolerate the drug at reduced dosage. Patients with rash or
hepatotoxicity have not been rechallenged. Uncommonly, vomiting,
bowel perforation, confusion, hallucinations, headache, sedation, and
euphoria have been reported. Flucytosine is teratogenic for rats and is
contraindicated in pregnancy.

Conversion of flucytosine to 5-fluorouracil in the human body
occurs in sufficient degree to be a possible explanation for toxicity to
bone marrow and the gastrointestinal tract.34 It is likely that the drug
is secreted into the gut, where flucytosine becomes deaminated by
intestinal bacteria and is reabsorbed as 5-fluorouracil.35 Flucytosine has a beneficial effect in patients with cryptococcosis,36 candidiasis, and chromoblastomycosis. It is not the drug of choice for
any infection because of the following: (1) its clinical efficacy in the
first two mycoses is inferior to that of amphotericin B; (2) primary
drug resistance is not uncommon in Candida infection; and (3)
secondary drug resistance is common in cryptococcosis and
chromoblastomycosis.

Flucytosine and amphotericin B are at least additive in their effects
in vitro and in mice experimentally infected with susceptible isolates
of Candida and Cryptococcus. Results with Aspergillus are contradic-
tory, with the combination never having shown to be better than an
optimum dose of amphotericin B alone.37,38 Flucytosine permitted a
lower dose of amphotericin B to be used to gain the same therapeutic
effect, and amphotericin B prevented the emergence of secondary drug
resistance. The same advantages have been confirmed in two large
multicenter studies of cryptococcal meningitis.39 The recommendation
that flucytosine be added during the first 2 weeks of IV amphotericin
B therapy for patients with AIDS and cryptococcal meningitis is based
on a retrospective analysis that showed that relapse is more frequent if
the patient subset permitted itraconazole.62 There was no advan-
tage for using flucytosine if the patient was subsequently given itra-
conazole. Considering that itraconazole is no longer advised for these
patients, the recommendation for the use of initial flucytosine is likely
to require an update.63 Experience with candidiasis remains limited.46

Flucytosine is more difficult to manage in patients with diminished
bone marrow reserve. Leukopenia and diarrhea are difficult to manage
in patients with AIDS, as is leukopenia and thrombocytopenia in
patients after bone marrow transplantation or patients with leukemia
or other hematologic malignancies. Oral flucytosine may not be reli-
ably administered to patients who are confused or vomiting. IV flucyto-
sine is no longer available in the United States but is used at the same
dose as the capsule formulation. The incidence of diarrhea or leuko-
penia is not lower with IV administration.

Flucytosine resistance has occurred, albeit uncommonly, during
combination therapy. Use of the combination in such patients incurs
the risk of toxicity without evidence that flucytosine adds to the thera-
peutic effect. Whenever flucytosine is used to treat a patient who has
received that drug before, the isolate should be tested for susceptibility.
In most laboratories, an MIC of 20 µg/mL or less is considered
susceptible.

Azole Antifungal Agents

GENERAL FEATURES

Mechanism of Action
The imidazole ring (see Fig. 40-1) confers antifungal activity on a
variety of synthetic organic compounds. Unlike the 5-nitroimidazoles,
such as metronidazole, activity against bacteria and protozoa, although
measurable, has not been clinically significant. Most of the imidazoles
reaching clinical trials have had similar in vitro activity against
most superficial and deep pathogens.57 Methods for in vitro suscepti-
bility testing are increasingly available as standardized tools. Standard-
ization has facilitated the establishment of clinically predictive
interpretive breakpoints for susceptibility testing results of Candida
species.58

N-substitution of imidazoles has created a family of drugs called
triazoles that have the same mechanism of action as the imidazoles, a
similar or broader spectrum of activity, and less effect on human sterol
synthesis. Both imidazoles and triazoles inhibit C-14α demethylation
of lanosterol in fungi by binding to one of the cytochrome P-450
enzymes, which leads to the accumulation of C-14α methyl sterols and
reduced concentrations of ergosterol, a sterol essential for a normal
fungal cytoplasmic membrane (see Fig. 40-2). Inhibition of cyto-
chrome P-450 also decreases the synthesis of testosterone and gluco-
corticoids in mammals, an effect seen clinically with ketoconazole but
not with later azoles. In studies of candidiasis, the principal pharmacodynamic driver for response to the triazole antifungal agents has been the ratio of total drug exposure (area under the curve) to the MIC. By studying cytochrome P-450 inhibition in vitro, new drugs can be selected that have better antifungal specificity. Some azoles, in addition to blocking ergosterol synthesis, have an immediate effect of damaging the fungal cytoplasmic membrane.

Because of their interaction with the P-450 system (including metabolism of the azoles by same), the azoles as a class have a significant number of drug-drug interactions. Fluconazole and posaconazole have the fewest significant interactions with itraconazole and voriconazole has many more. Key interactions are summarized in Table 40-1. Newer triazoles have properties that make them preferable to ketoconazole—not only less hormonal inhibition but also parenteral and oral formulations, a broader spectrum, better distribution into body fluids, less gastrointestinal distress, and less hepatotoxicity. For this reason, ketoconazole will not be included in the discussion that follows. The reader is referred to this chapter in prior editions of this text. The ideal triazole has not been developed because all have limitations and resistance to azoles in previously susceptible species is emerging. Resistance mechanisms include increased drug efflux and altered or increased C-14α-demethylase. The development of fluconazole resistance has been documented in C. albicans and increased resistance has been seen in Candida glabrata, C. krusei, C. glabrata, Candida norvegensis, and Candida inconspicua are intrinsically more resistant to azoles. Increased isolation of C. glabrata and C. krusei has been observed in patients receiving long-term azoles. Isolates resistant to fluconazole are variably cross-resistant to other azoles.4

**ITRACONAZOLE**

**Formulations and Pharmacology.** Itraconazole (Sporanox) is marketed as a 100-mg capsule, as an oral suspension of 100 mg/10 mL in cycloextrin, an oligosaccharide ring, and, formerly, as a solution in cycloextrin for IV administration. The ring entraps the hydrophobic water-insoluble drug. The drug is thus made soluble and is then released either at the lipid membrane of the enterocyte after oral administration or directly into tissues after IV administration. The solution makes possible delivery of the drug through a nasogastric tube in intubated patients and makes dosing of infants and small children more convenient. Oral absorption of the capsule is significantly enhanced by food, although absorption of the solution is best on an empty stomach. Bioavailability of the capsule is 55% when ingested after breakfast and the area under the time-concentration curve is increased 30% if the capsules are taken with food or if the solution is used. Bioavailability increases a further 25% to 30% with the solution in a fasting state. Co-administration of a cola beverage with itraconazole capsules almost doubled the area under the concentration versus time curve (AUC). Peak levels with either preparation are achieved 4 to 6 hours after a dose. Steady state is achieved only after 13 to 15 days, at which time the β-elimination half-life is about 19 to 22 hours. Absorption of the capsules in patients with AIDS is about half that in normal volunteers. Absorption of the capsule is markedly depressed in bone marrow transplant recipients, probably because of hypochlorhydria, mucositis, and graft-versus-host intestinal changes, but the depressed absorption can be alleviated by using the solution. For deep mycoses, an initial itraconazole dosage of 200 mg three times daily is recommended for the first 3 days to achieve high serum and tissue levels quickly. Hydroxyitraconazole, a metabolite of itraconazole, appears in blood in amounts roughly twice that of the parent drug and has antifungal activity and pharmacokinetics similar to those of the parent compound.7,8

Therapeutic blood level monitoring is useful to confirm adequate exposure. Because the existence of the active metabolite causes bioassays of itraconazole to give much higher concentrations than high-pressure liquid chromatography (HPLC), the difference follows from the susceptibility of the bioassay organism to hydroxyitraconazole, interpretation of the results depends on the method used. Target levels of the parent (unmetabolized) itraconazole molecule of 500 ng/mL by HPLC generally appear adequate, especially for prophylactic usage. A 1000-ng/mL target for the parent and its bioactive metabolite by bioassay also seem adequate. Limited data suggest that levels of 1000 ng/mL by HPLC might be preferred for proven infection.92

Tissue, pus, and bronchial secretion concentrations of itraconazole are generally higher than plasma concentrations, but cerebrospinal fluid concentrations are usually unmeasurable, even in patients with meningitis. Ocular levels are low. Saliva concentrations persist for 8 hours after the solution is administered and provide a possible benefit in treating oral disease or eradicating oral colonization. The drug is metabolized in the liver and excreted in feces as metabolites. Of the cycloexetrin liquid administered, 50% to 60% is secreted intact in feces, with most of the remainder broken down by gut bacteria among these; less than 0.3% is absorbed. No significant amount of bioactive itraconazole appears in urine. Plasma concentrations do not increase in patients with renal insufficiency or decrease with hemodialysis. The half-life is prolonged in those with cirrhosis. About 99% of serum itraconazole is bound to plasma proteins.

**Adverse Effects.** The most common adverse effect is dose-related nausea and abdominal discomfort, but symptoms rarely necessitate stopping therapy. Dividing the dose into twice-daily administration improves tolerance and absorption. Hypokalemia and edema may occur at 400 mg/day or higher dosages. Allergic rash is seen occasionally. Therapy is contraindicated during pregnancy and in nursing mothers. Itraconazole is infrequently hepatotoxic and does not suppress adrenal or testicular function at the dosages recommended. Flavoring in the solution somewhat ameliorates the unpleasant taste of cycloexetrin. Diarrhea, nausea, and other gastrointestinal complaints are more frequent with the solution. This increased toxicity is probably caused by the osmotic effect or bile salt complexing by unmetabolized cycloexetrin.

**Interactions.** As noted earlier (“Aazole Antifungal Agents: Mechanism of Action”), itraconazole has many clinically relevant drug-drug interactions. Key interactions are summarized in Table 40-1.

**Uses.** Itraconazole is useful for treatment of invasive aspergillosis, allergic bronchopulmonary aspergillosis, blastomycosis, histoplasmosis, meningitis, and nomenclature in coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, and phaeohyphomycosis, ringworm, including onychomycosis, and tinea versicolor. Itraconazole is also useful for the prevention of relapse in AIDS patients with disseminated histoplasmosis. Itraconazole suspension may be useful for prophylaxis against fungal infections during neutropenia, and possibly reduced the rate of invasive aspergillosis in one study. A comparison of itraconazole with amphotericin B as therapy of persistent fever in 384 neutropenic patients (56% of whom had acute myelogenous leukemia and 38% of whom had undergone marrow transplantation) found that IV itraconazole (which is no longer manufactured) followed by oral itraconazole was similarly effective and less toxic. The solution shows promise for the treatment of oral and esophageal candidiasis when used at 100 to 200 mg daily. Leishmania major infections respond poorly.

**FLUCONAZOLE**

**Formulations and Pharmacology.** Fluconazole (Diflucan) is currently available in 50-, 100-, 150-, and 200-mg tablets, a powder for oral suspension, and an IV formulation of 200 or 400 mg, both as 2 mg/mL. Fluconazole is well absorbed from the gastrointestinal tract. After ingestion of fluconazole, more than 80% of the drug can be found in the circulation. Of the oral dose, 60% to 75% appears unchanged in the urine and 8% to 10% appears unchanged in the feces. Oral absorption is not decreased in patients with AIDS or patients taking H2 blocking agents. Only 11% of serum fluconazole is protein-bound.
Concentrations of fluconazole in cerebrospinal fluid are approximately 70% of simultaneous blood levels, whether or not the meninges are inflamed and the drug penetrates into the brain. Penetration into saliva, sputum, urine, and other body fluids has also been excellent. Local instillation into the cerebrospinal fluid, bladder, or another site is unnecessary because of excellent penetration of the drug into body compartments.

The half-life in patients with normal renal function is 27 to 34 hours and increases to 59 and 98 hours in those with creatinine clearances of 35 and 14 mL/min, respectively. According to the manufacturer, the normal dose should be reduced to 50% when the creatinine clearance is reduced to 50 mL/min and to 25% when creatinine clearance is below 20 mL/min. A loading dose of twice the daily dose is recommended. Patients receiving hemodialysis should have one daily dose after each session. A dose of 6 mg/kg every 3 days has been advocated for premature infants in the first week of life, with dosing every 2 days during the second week of life.

**Drug Interactions.** As noted earlier ("Azole Antifungal Agents: Mechanism of Action"), fluconazole has a moderate number of clinically relevant drug-drug interactions. Key interactions are summarized in Table 40-1.

**Side Effects.** Adverse effects are uncommon. Even with chronic therapy, including dosages exceeding 400 mg/day, headache, hair loss, and anorexia were the most common symptoms, each occurring in 3%

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**TABLE 40-1 Azole Drug-Drug Interactions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Itraconazole*</th>
<th>Posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Azole Causes Increased Blood Levels of Other Drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allentanil</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astemizole</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
</tr>
<tr>
<td>Coumarin-type anticoagulants</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Yes'</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (&quot;statins&quot;)</td>
<td>Yes'</td>
<td>Yes'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levactemethylad (levomethadyl)</td>
<td>Yes'</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Midazolam (and other short-acting benzodiazepines)</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hypoglycemics (e.g., tolbutamide, glyburide, glipizide)</td>
<td>Yes'</td>
<td>Yes</td>
<td>Yes</td>
<td>No for glipizide</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Yes</td>
<td>Yes'</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Saquinavir and other protease inhibitors</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Yes</td>
<td>Yes'</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes'</td>
<td>Yes</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B. Azole Level Reduced by Other Drug**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Itraconazole*</th>
<th>Posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids of any type, including proton pump inhibitors</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes for cimetidine, no for others</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
<td>Yes'</td>
</tr>
<tr>
<td>Long-acting barbiturates</td>
<td>Yes'</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Yes</td>
<td>Yes'</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Yes</td>
<td>Yes'</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>St. John's wort</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Azoles are involved in drug-drug interactions either by interfering with metabolism and thus increasing the concentration of other drugs (Table 40-1A) or by having their level reduced via induction of hepatic metabolism or reduced absorption (Table 40-1B). The principal interactions are via CYP3A4 (all azoles) plus CYP2C9 (fluconazole, voriconazole) and CYP2C19 (fluconazole, voriconazole).

Key interactions found in the U.S. prescribing information are summarized here; more exhaustive reviews have been published. In addition, itraconazole levels are increased by clarithromycin, erythromycin, indinavir, and ritonavir. Absolute contraindication. Concomitant usage requires unusually careful dose adjustments and monitoring.
of patients, whereas 10% had rises in aspartate aminotransferase levels. Alopecia is reversible, even in some cases when the drug is continued at lower doses. Neurotoxicity has been described after heroic doses of 2000 mg daily. Rarely, anaphylaxis after the first dose or Stevens-Johnson syndrome has been observed.

**Indications**

**Candidiasis.** Fluconazole, 50 to 100 mg once daily, is one of the most effective agents for the treatment of oropharyngeal candidiasis. Daily doses of 100 mg are effective for esophageal candidiasis. A single dose of 150 mg is approximately as effective as topical treatment of vulvovaginal candidiasis. Patients with candidemia who are not neutropenic or otherwise seriously immunosuppressed respond as well to IV fluconazole therapy as to amphotericin B, provided that they do not have fluconazole-resistant Candida infection. A study comparing fluconazole with a combination of fluconazole plus amphotericin as initial therapy of candidemia has suggested that the combination might produce more rapid clearance of the bloodstream, but this result was confounded by differences in severity of illness between the two study groups. Although lacking the proof of a randomized trial, changing potentially infected central IV catheters in candidemic patients is thought by most authorities to be an important part of therapy. In a small number of patients with Candida endocarditis, long-term fluconazole therapy has been used to prevent relapse after amphotericin B therapy. For immunosuppressed patients and rapidly progressing or severely ill patients with deep candidiasis, amphotericin B or caspofungin would be preferred.

**Cryptococcal Meningitis.** Fluconazole has been used for the initial treatment of AIDS patients with cryptococcal meningitis who are neurologically intact and judged to have a good prognosis. Many authorities recommend amphotericin B or amphotericin B plus flucytosine for at least the first 2 weeks. Therapy can be changed to fluconazole, 400 mg daily for 2 months, if the patient has remained clinically stable. The propensity of AIDS patients to relapse has led to lifelong maintenance therapy with fluconazole, 200 mg daily. Patients who have achieved an increase in CD4+ count to at least 200/mm³ for a sustained period, perhaps 6 months, and who have no signs or symptoms of cryptococcal meningitis may have their maintenance therapy discontinued. If the CD4+ count subsequently falls below 200/mm³, maintenance therapy should be resumed.

**Prophylaxis in Patients with Acquired Immunodeficiency Syndrome.** Fluconazole, 200 or 400 mg once weekly, has reduced the incidence of oral and vulvovaginal candidiasis in patients with advanced HIV infection, but this regimen has not been demonstrated to prevent histoplasmosis, cryptococcosis, or esophageal candidiasis in this population. Prophylaxis with 200 mg daily reduces the incidence of oropharyngeal and esophageal candidiasis and cryptococcosis in patients with a CD4+ count below 200/mm³. Cost, lack of effect on survival, and the possibility of azole resistance has led the U.S. Public Health Service-Infectious Disease Society of America advisory committee to recommend against fluconazole prophylaxis in AIDS patients. Fluconazole is an alternative to itraconazole for maintenance therapy in AIDS patients with prior disseminated histoplasmosis.

**Prophylaxis in Preterm Neonates.** Fluconazole, 3 to 6 mg/kg, every third day for the first 2 weeks of life, and then every day until day 30 of life (neonates weighing 1000 to 1500 g at birth) or day 45 (neonates weighing less than 1000 g at birth) has reduced the rate of invasive candidial infection from 13% (placebo) to 2.7% (6-mg group) and 3.8% (3-mg group) in a randomized multicenter study of 322 evaluable infants. When compared with prior studies, these data suggest that neonatal units might consider the use of fluconazole prophylaxis in addition to standard infection control procedures.

**VORICONAZOLE**

**Formulations and Pharmacology.** Voriconazole (Vfend) is marketed as a 50- or 200-mg tablet, and as a solution in sulfobutyl ether β-cyclodextrin for intravenous administration. The oral bioavailability of voriconazole is approximately 96% and plasma protein binding is approximately 58%. Detailed tissue distribution data are not available, but voriconazole’s volume of distribution (4.6 L/kg) greatly exceeds that of water, thus suggesting extensive distribution into tissues. Voriconazole is cleared by hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. Hepatic clearance is via the cytochrome P-450 system. Voriconazole exhibits significantly nonlinear pharmacokinetics because of saturation of the clearance pathways at higher doses. The principal enzyme involved in clearance is CYP2C19 which has significant genetic polymorphisms that permit any given individual to be a homozygous extensive metabolizer, homozygous poor metabolizer, or heterozygous intermediate metabolizer. A heterozygous metabolizer will have, on average, a twofold higher total voriconazole exposure relative to a homozygous extensive metabolizer. A homozygous poor metabolizer will have a fourfold higher drug exposure on average; 15% to 20% of Asians but only 3% to 5% of whites and blacks are homozygous poor metabolizers. Despite these differences in metabolism, the achieved plasma levels overlap across the three possible groups and dose adjustment based on genotype or racial group is not recommended. Usual trough concentrations are in the range of 0.5 to 5 mg/L, with considerable intraindividual variation. Therapeutic drug monitoring may be of use in settings in which systemic exposures are less well predicted (e.g., in combination with inducers of hepatic metabolism or in children).

Standard loading dosing regimens followed by maintenance doses that are 50% of normal are recommended for individuals with mild to moderate hepatic cirrhosis (Child-Pugh classes A and B). However, no data are available on rates of clearance in individuals with severe hepatic cirrhosis (Child-Pugh class C). Dosage adjustments are not required for renal dysfunction and voriconazole is not significantly
cleared by hemodialysis. Children aged 2 to 12 years have variably increased metabolism and may require higher doses. In one study, a dose of 4 mg/kg every 12 hours in the children was found to produce systemic exposures comparable to those produced by a dose of 3 mg/kg every 12 hours in adults. Initiation of therapy in children with 6 mg/kg 12h × 2 doses has been suggested.\textsuperscript{127,128} The European prescribing information for voriconazole has recently been updated to suggest that children aged 2 to 12 years should be treated twice daily with 7 mg/kg (IV) or 200 mg (PO).\textsuperscript{129} Data for children younger than 2 years were inadequate to permit dose selection.

**Drug Interactions.** As noted earlier ("Azole Antifungal Agents: Mechanism of Action"), voriconazole has many clinically relevant drug-drug interactions. Key interactions are summarized in Table 40-1.

**Side Effects.** Voriconazole is generally well tolerated and has a side effect profile that is largely similar to that of other triazoles.\textsuperscript{130} The most frequently reported adverse event is a visual disturbance that appears to be unique to voriconazole. In the clinical studies reported to date, approximately 30% of patients reported altered or enhanced light perception beginning approximately 30 minutes after a dose and lasting for approximately 30 minutes. The visual alteration is described as blurred vision, color vision change, and/or photophobia. The effect is mild, only rarely resulted in discontinuation of therapy, and was uniformly reversible. Despite extensive studies, the mechanism for this side effect is not known. Although the effect is usually transient, patients should be advised to avoid activities that require keen visual acuity while experiencing visual changes. Hallucinations and confusion have also been reported; hallucinations occurred in 12 of 72 patients in one study, were visual or auditory, and most often occurred in the first 24 hours of IV therapy at 6 mg/kg.\textsuperscript{131} Voriconazole can cause severe photosensitivity.\textsuperscript{132} Finally, voriconazole has been rarely associated with prolongation of the QT interval and torsade de pointes. These events have occurred in those with multiple proarrhythmic factors (e.g., cardiotoxic chemotherapy, cardiomyopathy, hypokalemia), and caution is thus recommended when voriconazole is given to these patients. In particular, electrolyte disturbances such as hypokalemia, hypomagnesemia, and hypocalcemia should be corrected before initiation of voriconazole therapy.

**Indications**

**Aspergillosis.** Voriconazole was licensed for treatment of invasive aspergillosis on the basis of a randomized, unblinded comparative trial in which patients with invasive aspergillosis were randomized to receive initial therapy with either voriconazole—two IV doses of 6 mg/kg on day 1, two intravenous 4 mg/kg doses daily for at least the next 7 days, and then 200 mg PO twice daily—or ABD, 1 to 1.5 mg/kg/day. Following initial randomization, patients could be switched to other licensed therapies as dictated by clinical events. After 12 weeks, 53% of the patient randomized to voriconazole but only 32% of those randomized to ABD had a successful outcome. In addition, the survival rate of the voriconazole group was 71% versus only 58% for those randomized to ABD. These results clearly demonstrate the efficacy of voriconazole for aspergillosis and its superiority over ABD, and are supported as well by data from open-label studies of therapy of aspergillosis with voriconazole.\textsuperscript{135}

**Other Mycoses.** Voriconazole is also licensed for treatment of invasive fusariosis and scedosporiosis based on data submitted to the U.S. Food and Drug Administration (FDA) showing a 43% (9 of 21 patients) and 63% (15 of 24 patients) response rate for these two diseases, respectively. Although not licensed for esophageal candidiasis, voriconazole (200 mg, twice daily PO) was at least as effective as fluconazole (200 mg, once daily) in a randomized and blinded trial but was more often associated with adverse events.\textsuperscript{136} A trial of voriconazole versus amphotericin B deoxycholate as therapy for invasive candidiasis has found that voriconazole is not inferior to amphotericin B deoxycholate.\textsuperscript{137} Efficacy in refractory candidiasis has also been reported.\textsuperscript{137,138}

**Fever and Neutropenia.** Voriconazole was compared with liposomal amphotericin B as empirical antifungal therapy for persistent fever in neutropenic cancer patients in a large open-label randomized study.\textsuperscript{139} The results were mixed, but the most conservative analyses found voriconazole to be possibly inferior to liposomal amphotericin B and the FDA did not approve voriconazole for this indication.\textsuperscript{140}

**POSACONAZOLE**

**Formulations and Pharmacology.** Posaconazole (Noxafil) is marketed as a 40-mg/mL suspension. The oral bioavailability of posaconazole is affected by food; nonfat and high-fat meals increase absorption by 2.6- and 4.0-fold, respectively.\textsuperscript{141,142} Although the half-life is approximately 35 hours and thus potentially consistent with daily dosing, exposure is further increased by dividing the daily dose, with the maximum AUC being achieved by four divided doses, each taken with a fatty meal.\textsuperscript{143} Posaconazole is lipophilic, more than 98% protein-bound, and has a volume of distribution much higher than body water (1774 L in adults).\textsuperscript{143} These data suggest extensive distribution and penetration into tissues. Posaconazole circulates primarily as the parent compound. Clearance is primarily by fecal excretion with only a minority (13%) excreted via renal clearance. Hepatic metabolism via uridine diphosphate (UDP) glucuronidation plays only a small role in clearance and cytochrome P-450 (CYP450)–mediated oxidation does not occur.\textsuperscript{144} Posaconazole is a substrate for p-glycoprotein. Posaconazole dosage is 200 mg (5 mL), three times daily, for prophylaxis of invasive fungal infection during neutropenia or moderate to severe graft-versus-host disease.\textsuperscript{144,145} For oropharyngeal candidiasis, posaconazole, 100 mg (2.5 mL) twice daily, is given on day 1 and then 100 mg daily × 13 days; the dosage may be increased to 400 mg twice daily for infections refractory to itraconazole or fluconazole. Dose adjustment is not required for renal insufficiency; the principal concern is that plasma exposures in this group are more variable and that inadequate exposures might result.\textsuperscript{145} Studies in hepatic insufficiency are limited and caution is advised, but dose adjustment is probably also not required in this setting.\textsuperscript{146} Therapeutic drug level monitoring is not currently recommended for this agent.\textsuperscript{145} The dosage for infants and children is not known, but limited data suggest similar pharmacology in older children.\textsuperscript{147}

**Drug Interactions.** As noted earlier ("Azole Antifungal Agents: Mechanism of Action"), posaconazole has a moderate number of clinically relevant drug-drug interactions. Key interactions are summarized in Table 40-1.

**Side Effects.** The tolerability of posaconazole is generally similar to that of fluconazole, with gastrointestinal symptoms and headache being the mostly common reported adverse events.\textsuperscript{148} Although all azoles have at least some predisposition to hepatic injury, significant hepatitis caused by posaconazole appears to be rare. Posaconazole did not prolong QT intervals in studies of volunteers, but caution should still be taken when administering to patients with potentially proarrhythmic conditions, and coadministration with proarrhythmic drugs metabolized by CPY3A4 should be avoided.\textsuperscript{149} Plasma levels have not been consistently linked to adverse events.

**Indications**

**Prophylaxis of Invasive Fungal Infection During Periods of Very High Risk.** Posaconazole, 200 mg three times daily, prevents fungal infections in high-risk patients during (1) graft-versus-host disease (GVHD) associated with allogeneic bone marrow transplantation and (2) the neutropenic period associated with myelosuppressive chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. In the study by Ullman and colleagues\textsuperscript{146} of prophylaxis during GVHD, posaconazole was similar to fluconazole in the rate of overall fungal infections, but was superior in the prevention of aspergillosis (2.4% vs. 7.0%) and prevention of breakthrough fungal infections (2.4% vs. 7.6%). In the study by Cornely and associates\textsuperscript{147} of prophylaxis during
chemotherapy, posaconazole was superior to standard regimens of either fluconazole or itraconazole in the prevention of invasive fungal infections in general (2% vs. 8%) and aspergillosis in particular (1% vs. 7%). Adverse events caused by posaconazole were more common in the study by Cornely and co-workers but occurred at similar rates to the comparator therapy in the study by Ullman and colleagues.

**Oropharyngeal Candidiasis.** In a report by Vazquez and associates, posaconazole (200 mg on day 1, 100 mg daily × 13 days thereafter) was as effective as fluconazole (same dosage regimen) in the treatment of oropharyngeal candidiasis in subjects with HIV-AIDS. Consistent with its long half-life, post-therapy mycologic suppression was somewhat better and clinical relapse was somewhat less frequent in the posaconazole-treated group. Refractory cases of posaconazole have been reported to respond effectively to extended courses (up to 3 months) of posaconazole, 400 mg twice daily. Extended therapy in this setting appears well tolerated.

**Therapy of Various Mold Infections.** Consistent with its in vitro activity against a broad range of yeast and mold fungi, a variety of less well-controlled studies have suggested its use for refractory aspergillosis, fusariosis, coccidioidomycosis, eumycetoma, and chromoblastomycosis. Therapy has generally been with 800 mg/day in divided doses. The long-term therapy often required in these settings appears well tolerated.

**INVESTIGATIONAL TRIAZOLES**

Isavuconazole, albaconazole, and ravuconazole are other triazoles currently in the later stages of development. All three appear to possess good antifungal spectra. Isavuconazole and ravuconazole have half-lives that may permit very infrequent dosing.

**Echinocandin Antifungal Agents**

**GENERAL FEATURES**

The echinocandin antifungal agents act by inhibiting the synthesis of 1,3-β-D-glucan. Along with 1,6-β-D-glucan, chitin (a polymer of N-acetylglucosamine), and cell wall proteins, 1,3-β-D-glucan is one of the fibrillar and interwoven macromolecules that form the fungal cell wall. 1,3-β-D-glucans are the predominant components of the cell wall of the ascomycetous fungi, provide much of the rigidity of the wall, and are synthesized by a transmembrane glucan synthase complex. Although the precise mechanism of action is unknown, the echinocandins inhibit the functioning of this complex (see Fig. 40-2). Disruption of 1,3-β-D-glucan synthesis leads to reduced wall integrity, abnormal cell morphology, and finally cell rupture and death. In studies to date of echinocandins as therapy for candidiasis, the principal pharmacodynamic driver of the in vivo response has been the ratio of the peak achieved concentration to the MIC.

There are now three licensed echinocandins, caspofungin, micafungin, and anidulafungin. These agents are much more similar than they are different. All are cyclic lipopeptides (see Fig. 40-1) that must be given intravenously and have very few drug interactions, an admirably low adverse event rate, and essentially identical antifungal spectra.

Caspofungin has the broadest array of approved indications and the most clinical data of the three products. Micafungin has the most detailed data on use in neonates and children. Anidulafungin appears to have somewhat fewer drug-drug interactions. Their in vitro activity is generally similar, especially when testing is performed in the presence of serum. The only direct comparison of any of the three has been a study of micafungin versus caspofungin for treatment of invasive candidiasis. The two drugs yielded essentially identical results.

The echinocandins are fungicidal for all Candida species, including isolates resistant to other agents. A paradoxical effect has been described in which the fungicidal activity of caspofungin against some isolates of C. albicans and C. dubliniensis disappears at higher concentrations. Attempts to demonstrate this effect in experimentally infected mice has been inconclusive. All echinocandins have somewhat reduced activity against isolates of C. parapsilosis and C. guilliermondii, but this lesser activity does not appear clinically relevant in studies reported to date. All are active against Aspergillus spp., but activity is limited to growing and dividing hyphal elements; resting forms are not killed. These agents are not active against C. neoformans or Trichosporon asahii and their activity against other fungi is variable, with complete resistance noted in many cases. Thus, these agents are presently limited to therapy of candidiasis and aspergillosis. Available susceptibility testing methods correlate with defined molecular resistance mechanisms and a consensus is emerging on detection of clinically relevant resistance. However, isolates with elevated MICs remain uncommon and susceptibility testing of clinical isolates has yet to become routine.

**CASPOFUNGIN**

**Formulations and Pharmacology.** Caspofungin (Cancidas) is marketed in 50- and 70-mg dose units as a powder to be reconstituted in water or saline for IV infusion. In a murine study, caspofungin tissue levels were higher than serum levels in liver and kidney; lower in the heart, brain, and thigh; and similar in lung and spleen. Caspofungin is 97% bound to serum albumin. The plasma kinetics of caspofungin are driven primarily by tissue distribution; metabolism is limited, and clearance of caspofungin occurs via a combination of spontaneous chemical degradation, hydrolysis, and N-acetylation. Dose adjustments are not required for renal function because caspofungin is neither excreted by the kidney nor cleared by hemodialysis. The clearance of caspofungin is modestly reduced in subjects with moderate hepatic insufficiency (Child-Pugh score of 7 to 9) and a dosage reduction from the usual daily dose of 50 to 35 mg/day is recommended. There are no data in individuals with more advanced hepatic insufficiency. The available data in children suggest the need for dosages slightly greater than those used in adults. A study of two pediatric liver transplant recipients has found that doses of 1 mg/kg/day appear appropriate, but a study of nine patients has suggested that 50 mg/m² would provide a systemic exposure similar to that produced in adults with 50 mg/day. Based on very limited data, neonates would be treated with 1 mg/kg/day × two doses and then 2 mg/kg daily.

**Drug Interactions.** Caspofungin is not an inhibitor or inducer of the hepatic cytochrome metabolism enzymes and has few meaningful drug-drug interactions. Cyclosporine co-administration increases caspofungin exposure and has been associated with increased hepatic transaminase levels in volunteers. As a consequence, concomitant usage of caspofungin and cyclosporine is not recommended unless the potential benefit outweighs the potential risk to the patient. Caspofungin co-administration reduces tacrolimus exposure by approximately 20% and dosage adjustments may be required. Rifampin reduces caspofungin blood levels by approximately 30% and the daily dosage of caspofungin should be increased from 50 to 70 mg if these drugs are co-administered. Similarly, limited data with other inducers of drug clearance (e.g., efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine) have suggested that reduced caspofungin levels are possible and that an increase in the daily dosage to 70 mg should be considered.

**Side Effects.** Adverse reactions with caspofungin have overall been infrequent and minor. Symptoms possibly related to histamine release have been reported. Caspofungin does not appear to be significantly hepatotoxic or nephrotoxic.

**Indications**

**Candidiasis.** Caspofungin is indicated for the treatment of invasive candidiasis and esophageal candidiasis. These indications were based primarily on a randomized, double-blind, placebo-controlled comparison of caspofungin (70-mg loading dose following by 50 mg daily)
versus ABD (0.6 to 1.0 mg/kg/day) as therapy for invasive candidiasis in adults, with 80% of the subjects enrolled for candidemia.173 Both study arms permitted a switch to oral fluconazole after 10 days of IV therapy. The success rates showed a trend favoring caspofungin (73% success) over amphotericin B (62%), with far fewer adverse events noted in the caspofungin-treated group. Responses for the two study regimens were similar for each of the Candida species causing meaningful numbers of infections (C. albicans, C. parapsilosis, C. tropicalis, and C. glabrata). The results are entirely consistent with the efficacy and safety data shown in three related studies of caspofungin as therapy for esophageal candidiasis,174-176 including disease caused by fluconazole-resistant isolates.177

Aspergillosis. Caspofungin is also licensed as therapy for invasive aspergillosis in patients who are refractory to or intolerant of other therapies. The dosage is the same as for candidiasis. This indication is based on a series of open-label cases of proven invasive aspergillosis.181,182 An overall success rate of approximately 40% was reported in a series of patients in whom neutropenia, malignancy, and concomitant immunosuppressive therapy were common. Subsequent reports have provided further open-label monotherapy179,180 and open-label combination experience179,180 documenting response rates in the same range.

Empirical Therapy of Presumed Fungal Infections in Febrile, Neutropenic Patients. Caspofungin was noninferior to liposomal amphotericin B in a large comparative study of treatment of adults with persistent fever and neutropenia.183 Caspofungin showed a better response rate in the subset of patients who were proven in retrospect to have had a fungal infection (52% vs. 26% response), with the effect principally the result of a better response in cases of documented aspergillosis. Caspofungin was overall better tolerated than liposomal amphotericin B.

ANIDULAFUNGIN

Formulations and Pharmacology. Anidulafungin (Eraxis) is marketed in 50- and 100-mg dose units as a powder to be reconstituted in an ethanol-based diluent provided with the powder.184 The amount of ethanol is low enough not to have a clinical effect. Anidulafungin is more than 99% bound to plasma proteins. Distribution from the circulation occurs quickly into a volume of distribution (30 to 50 L) that is similar to total body fluid volume. Anidulafungin is slowly degraded by the chemical opening of its ring structure.185 Dose adjustments are not required for renal insufficiency, hepatic insufficiency, age, or gender. In pediatric (age, 2 to 11 years) and adolescent (age, 12 to 17 years) children, doses of 0.75 mg/kg/day and 1.5 mg/kg/day produced blood levels similar to those achieved in adults with 50- and 100-mg/day doses.186

Drug Interactions. Anidulafungin has no meaningful CYP450 enzyme interactions: it is not an inducer, inhibitor, or substrate and has no interaction with either drugs cleared by these pathways or with drugs that induced these pathways.184 Specifically, dose adjustments or special precautions are not needed during co-administration of cyclosporine, voriconazole, tacrolimus, liposomal amphotericin B, or rifampin.184

Side Effects. Histamine-mediated symptoms (e.g., rash, urticaria, flushing, pruritus, dyspnea, hypotension) have been noted on occasion but are infrequent when the rate of infusion does not exceed 1.1 mg/min.184 Adverse reactions with anidulafungin have otherwise generally been infrequent, minor, and comparable to those observed with fluconazole. Anidulafungin is not significantly hepatotoxic or nephrotoxic.

Indications

Candidiasis. Anidulafungin is indicated for the treatment of invasive candidiasis and of esophageal candidiasis. In the key study of invasive candidiasis,187 anidulafungin (200 mg on day 1 and then 100 mg/day) was compared with fluconazole (800 mg on day 1 followed by 400 mg daily). Success rates at the end of IV therapy were significantly higher with anidulafungin than fluconazole (76% vs. 60%). The superiority of anidulafungin was particularly marked in one center; removing the results from this one center removed the statistical significance of inferiority. However, these data are supported by similar response rates in a smaller dose–ranging study in invasive candidiasis.188 Anidulafungin (100 mg on day 1 and then 50 mg/day) was found to be noninferior to fluconazole (200 mg PO on day 1 and then 100 mg PO/day) in esophageal candidiasis, with success rates more than 97% for both arms. The safety profile of anidulafungin was essentially the same as that of fluconazole in the comparative studies.

Use in Other Settings. Anidulafungin is active in vitro against Aspergillus spp. but data on its clinical usefulness against this fungus have not been reported. Similarly, study results have not as yet been reported on its use as a prophylactic agent during periods of risk for invasive aspergillosis or candidiasis or as empirical therapy for persistently febrile neutropenic patients.

MICAFUNGIN

Formulations and Pharmacology. Micafungin (Mycamine) is marketed in 50- and 100-mg dose units for reconstitution in saline.189 Micafungin is more than 99.5% bound to serum proteins (mostly albumin) and its volume of distribution approximates that of body water.190 Micafungin undergoes a small amount of metabolic transformation, but the primary route of elimination is via fecal excretion. Dose adjustments are not required based on race, gender, renal function (any severity), or hepatic dysfunction (mild and moderate).191 No data are available for cases of severe hepatic dysfunction. In children ages 2 to 8 years, micafungin has a somewhat higher clearance and volume of distribution than in older children or adults.191,192 Overall, a dose of 2 mg/kg/day appears appropriate for both premature infants and older children and has been associated with good clinical responses.193

Drug Interactions. Micafungin does not have any meaningful interactions with the hepatic oxidative CYP450 enzymes—it does not induce any of these enzymes and is only minimally metabolized by an inhibitor of CYP3A. Furthermore, micafungin lacks interactions with the P-glycoprotein transport system. Based on specific drug-drug interactions studies conducted by the drug sponsor, no dose adjustments are required when micafungin is co-administered with myco- phenolate mofetil, cyclosporine, tacrolimus, prednisolone, fluconazole, voriconazole, amphotericin B, ritonavir, or rifampin. As judged by the AUC, micafungin increases the systemic exposure of itraconazole, nifedipine, and sirolimus by about 20%. Dose adjustment is not routinely needed for these three agents, but patients should be monitored closely for toxicity.193,194

Side Effects. Adverse reactions with micafungin have generally been infrequent and minor,194 even at very high doses.193,194 Histamine release-related symptoms (e.g., pruri carsis, facial swelling, vasodilation) have been reported. Micafungin does not appear to be significantly hepatotoxic or nephrotoxic.

Indications

Candidiasis. Based on randomized161,196 and open-label data,197 micafungin is indicated at 100 mg/day for the treatment of invasive candidiasis. In the study by Kuse and co-workers,196 micafungin (100 mg/day) was noninferior to liposomal amphotericin B (3 mg/kg/day; success rates of 90% for both arms), with fewer drug-related adverse events seen in the micafungin arm. Similarly, a three-way comparison of micafungin (dose groups at 100 and 150 mg/day) with caspofungin (70 mg on day 1, 50 mg/day on subsequent days) found similar response rates (76%, 71%, and 72%) across the three arms.190 Adverse
event rates were similar for the caspofungin and micafungin arms. Finally, a comparison of micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) as treatment of invasive candidiasis in premature infants and older children found similar response rates of 73% and 76%, respectively.135

Based on a pair of studies by de Wet and associates,198,199 micafungin is also registered for the treatment of esophageal candidiasis at a dosage of 150 mg/day.

Prophylaxis of Candidal Infections in Hematopoietic Stem Cell Transplant Recipients. Based on a study reported by van Burik and co-workers,200 micafungin is registered for use at 50 mg/day during the at-risk period following hematopoietic stem cell transplantation. In this study, micafungin was compared with fluconazole (400 mg/day). The level of risk for infection varied substantially across the study group: about half of the enrolled subjects had received an allogeneic transplant and half had received an autologous transplant. Subjects were treated for a median of only 19 days and the rate of proven fungal infection was similar and low (2%) in both arms. Adverse events were similar for the two study groups.

Use in Other Settings. Micafungin is active in vitro against Aspergillus spp. but only a small amount of open-label monotherapy data on its clinical usefulness against this fungus have been reported.200,201 Similarly, studies have not as yet been reported on its use as empirical therapy for persistently febrile neutropenic patients.

INVESTIGATIONAL ECHINOCANDINS

Aminocandin is an investigational agent with a half-life that may permit dosing less often than once daily.155 It otherwise appears similar to the three licensed echinocandins.

Other Agents

Drugs still being evaluated in preclinical studies include sordarins (inhibit protein synthesis by their effect on fungal elongation factor 2), nikkomycin Z (inhibits chitin synthesis), and various peptides with unknown mechanisms of action.156 Immunomodulators hold promise, but insufficient clinical data exist to determine where and how these drugs might be used.204

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