

Current Options in Antifungal Pharmacotherapy

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Infections caused by yeasts and molds continue to be associated with high rates of morbidity and mortality in both immunocompromised and immunocompetent patients. Many antifungal drugs have been developed over the past 15 years to aid in the management of these infections. However, treatment is still not optimal, as the epidemiology of the fungal infections continues to change and the available antifungal agents have varying toxicities and drug-interaction potential. Several investigational antifungal drugs, as well as nonantifungal drugs, show promise for the management of these infections.

Key Words: antifungal drugs, invasive fungal infection, amphotericin B, polyenes, invasive aspergillosis, liposomal amphotericin B, L-AmB.
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OUTLINE

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Icofungipen Conclusion

Invasive fungal infections continue to be associated with high rates of morbidity and mortality in both immunocompromised and immunocompetent hosts. Amphotericin B deoxycholate (AmBd) has been the cornerstone for treatment of invasive fungal infections since the early 1950s. However, new agents have emerged to manage these infections over the past 15 years (Figure 1). Although *Candida* species remain the most common pathogens associated with fungal disease, infections caused by *Aspergillus* and *Cryptococcus* sp, Zygomycetes, and the endemic fungi (*Histoplasma*, *Blastomyces*, and *Coccidioides* sp) also account for many fungal infections.

Candida species have been associated with a wide spectrum of invasive disease, from catheter-associated infections to widespread disseminated disease; reported attributable mortality rates are 10–70% in patients with nosocomial candidemia.^{1–3} Empiric antifungal therapy delayed by as little as 12 hours has been associated with increased mortality.^{4,5} The term invasive candidiasis has been used to collectively describe the severe forms of disease, excluding uncomplicated candiduria and oropharyngeal and esophageal candidiasis.⁶

Identifying patients at risk for development of *Candida* infections is an important step in deciding which patients should receive treatment.⁷

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This treatment may include strategies that are either presumptive (index of suspicion is high due to many risk factors) or prophylactic (aimed at disease prevention in high-risk patients).⁸ Prolonged stay in the intensive care unit (ICU), placement of central venous catheters, prolonged treatment with broad-spectrum antibiotics, receipt of parenteral nutrition, recent surgery (particularly intraabdominal), hemodialysis, and a diagnosis of diabetes mellitus or pancreatitis have been identified as risk factors for invasive candidiasis.⁹

Selection of antifungal therapy for invasive candidiasis may be influenced by changes in local epidemiology. Over the past 10 years, a shift in species distribution has favored non-*albicans* *Candida* species.^{10, 11} Some evidence indicates that fluconazole use has driven this shift¹²; however, other evidence has not been able to link previous fluconazole use with the emergence of non-*albicans* species.¹³ In an antifungal susceptibility survey of over 2000 bloodstream isolates of *Candida* species, *C. glabrata*, which is less susceptible to fluconazole in vitro than other species, accounted for 23% of the *Candida* bloodstream isolates; *C. krusei*, which is completely resistant to fluconazole, accounted for 3%.¹⁴ However, such findings may vary by institution.

In addition, *C. parapsilosis*, which typically demonstrates higher minimum inhibitory concentrations (MICs) in vitro than other *Candida* species against echinocandins, accounted for 20% of the isolates causing bloodstream infections.

Aspergillus, a genus of mold ubiquitous in the environment, can cause invasive fungal infections in nearly every organ in the immunocompromised host, but the pulmonary system is most commonly affected.¹⁵ The true attributable mortality rate for invasive aspergillosis is not known. However, historical data reporting a crude mortality rate of 90% clearly no longer represent the current rate in the era of allogeneic hematopoietic stem cell transplantation (HSCT), in which nonmyeloablative chemotherapy and antifungal prophylaxis are administered.¹⁶ More recent studies have suggested a shift of aspergillosis to late-onset infection with a more indolent course and significantly lower all-cause and attributable mortality rates.^{17, 18}

A definitive diagnosis of invasive aspergillosis requires either a positive culture from a sterile site or, in the absence of a positive culture, histologic or radiologic evidence in a patient at high risk with compatible clinical findings.¹⁹ When the organism is ultimately identified in tissues, the disease may be too advanced for

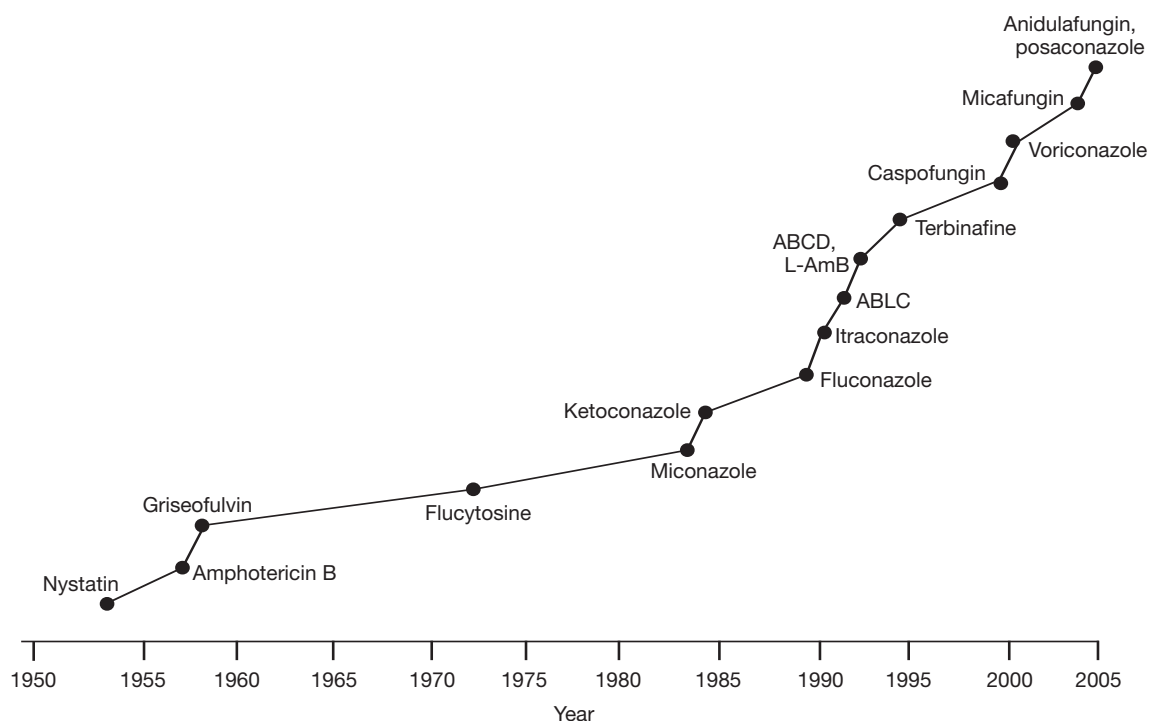


Figure 1. Development of antifungal drugs from 1954–2007. ABCD = amphotericin B colloidal dispersion; L-AmB = liposomal amphotericin B; ABLC = amphotericin B lipid complex.

successful treatment.²⁰ Thus, tools for early diagnosis, preventive strategies, and new agents for treatment of the disease are needed to reduce overall mortality in patients with invasive aspergillosis.²¹

Cryptococcus neoformans is an encapsulated yeast that causes disease primarily of the central nervous system (CNS) and respiratory system.²² The incidence of disease is 0.4–1.3 cases/100,000 persons in the general population and 2–7 cases/1000 patients with acquired immunodeficiency syndrome (AIDS).²³ In addition, patients who have undergone organ transplantation and are receiving high-dose corticosteroids are at increased risk for development of cryptococcosis.²⁴ Overall mortality in patients with cryptococcal meningitis may be as high as 30%, and even after an initial cure, 40% of patients have residual neurologic deficits.²⁵ Patients with AIDS, in whom the cryptococcal infection may never be cured, may require prolonged secondary prophylaxis.²⁶

Zygomycosis is a group of fungal infections caused by organisms such as *Rhizopus*, *Absidia*, and *Mucor*. Zygomycetes can cause disseminated disease; however, disease of the pulmonary system and paranasal sinuses with extension to the brain are the most common.²⁷ Diabetes and immunosuppression (e.g., hematologic malignancies with profound neutropenia) are the primary risk factors for patients with zygomycosis.²⁸ A definitive diagnosis of zygomycosis is made by demonstration of tissue invasion on histopathologic examination at the infection site with or without microbiologic evidence of the fungus from the same site. The prognosis for patients with zygomycosis is poor, and aggressive early diagnosis and treatment are critical for improving outcomes.

Histoplasma capsulatum, *Blastomyces dermatitidis*, and *Coccidioides immitis* are the major endemic fungi that can cause disease in humans. They are referred to as dimorphic fungi because they can grow in a mycelial form when incubated at 25°C (room temperature) or in a yeast form in human tissue or when incubated at 37°C. These organisms can cause disseminated disease, often by way of a primary pulmonary infection that may be asymptomatic. They can be associated with either acute or chronic infections.²⁹ Infections caused by *Histoplasma* and *Blastomyces* species typically cluster within the Ohio and Mississippi River valleys, whereas those caused by *Coccidioides* cluster within the southwestern United States. However, other pockets of endemicity have been reported.

Although infections caused by endemic mycoses are not required to be reported to authorities, estimates are that approximately 100,000 cases of coccidioidomycosis³⁰ and 1–2 cases of blastomycosis/100,000 persons in the general population occur annually in the geographic areas where the organisms are endemic.³¹ In addition, an estimated 10–25% of patients with human immunodeficiency virus (HIV) infection develop disseminated histoplasmosis; however, environmental exposure and primary antifungal prophylaxis may affect prevalence.²⁶

Many antifungal agents are used to treat patients with known or presumed invasive fungal infections and those at high risk for such infections. In addition, several investigational antifungal drugs as well as nonantifungal drugs are being studied for their management of these infections. This article focuses on the use of these agents as monotherapy because combination antifungal therapy has been reviewed in detail elsewhere.³²

Polyenes

Although more than 200 polyene antibiotics have been identified, amphotericin B and nystatin are the only polyenes used routinely in the clinical setting. In 1957, amphotericin B was the first antifungal agent approved by the United States Food and Drug Administration (FDA) for systemic administration. This agent was the mainstay of antifungal treatment for invasive fungal infections until triazoles and echinocandins became available in recent years. Three commercially available lipid formulations of amphotericin B—amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-AmB)—have demonstrated efficacy.

Compound formulations of amphotericin B in lipid emulsions are not recommended. Nystatin is formulated for topical applications because systemic administration is too toxic for humans. A liposomal preparation of nystatin, which could enable systemic delivery of this compound to humans, had been investigated in clinical trials of invasive fungal infection; however, it was not under development at the time of this writing. Thus it is not discussed further.

Mechanism of Action

Polyenes target the fungal cytoplasmic membrane by interaction with sterols in the fungal cell membrane to create nonaqueous and aqueous channels (Figure 2).³³ Cellular components such

as potassium then leak through the pores, resulting in loss of membrane potential and subsequent collapse.³⁴ At low concentrations of amphotericin B, the channels are permeable only to monovalent cations such as potassium. At high concentrations of amphotericin B, the nonaqueous channels interact with ergosterol or cholesterol in the cell membrane to form aqueous pores that are permeable to chloride and potassium. This results in increased permeability to H^+/OH^- , intracellular acidification, and subsequent membrane damage.

Amphotericin B has more affinity for ergosterol, the primary sterol of the fungal cell membrane, than for cholesterol, which comprises the human cell membranes. Binding of amphotericin B to cholesterol in mammalian cells leads to cellular toxicity and adverse events.³⁵

Other mechanisms of action for polyenes against fungi have been reported, including damage to cell walls at concentrations below the MIC, immunomodulatory effects, and oxidative damage.^{36, 37}

Clinical Efficacy

The efficacy of amphotericin B has been estab-

lished after decades of clinical use as well as controlled clinical trials involving numerous fungal infections. Lipid formulations of amphotericin B are generally considered interchangeable with AmBd; studies have suggested that these formulations have efficacy similar to or, in some cases, better than that of AmBd.^{38, 39}

Candidiasis

Amphotericin B has demonstrated efficacy as treatment for a variety of invasive infections caused by *Candida* species, including fungemia, osteomyelitis, chronic disseminated candidiasis, endocarditis, and endophthalmitis. The activity of AmBd in candidemia and other forms of invasive candidiasis has been established in several clinical trials.^{40–43} The fungicidal activity of amphotericin B is often preferred for patients with more difficult and challenging infections, particularly those with neutropenia or critical illness and when the organism has not been identified to the species level. For these patients, AmBd 0.7 mg/kg/day or greater is preferred.

Although AmBd is efficacious, its associated renal toxicity can complicate therapy, particularly

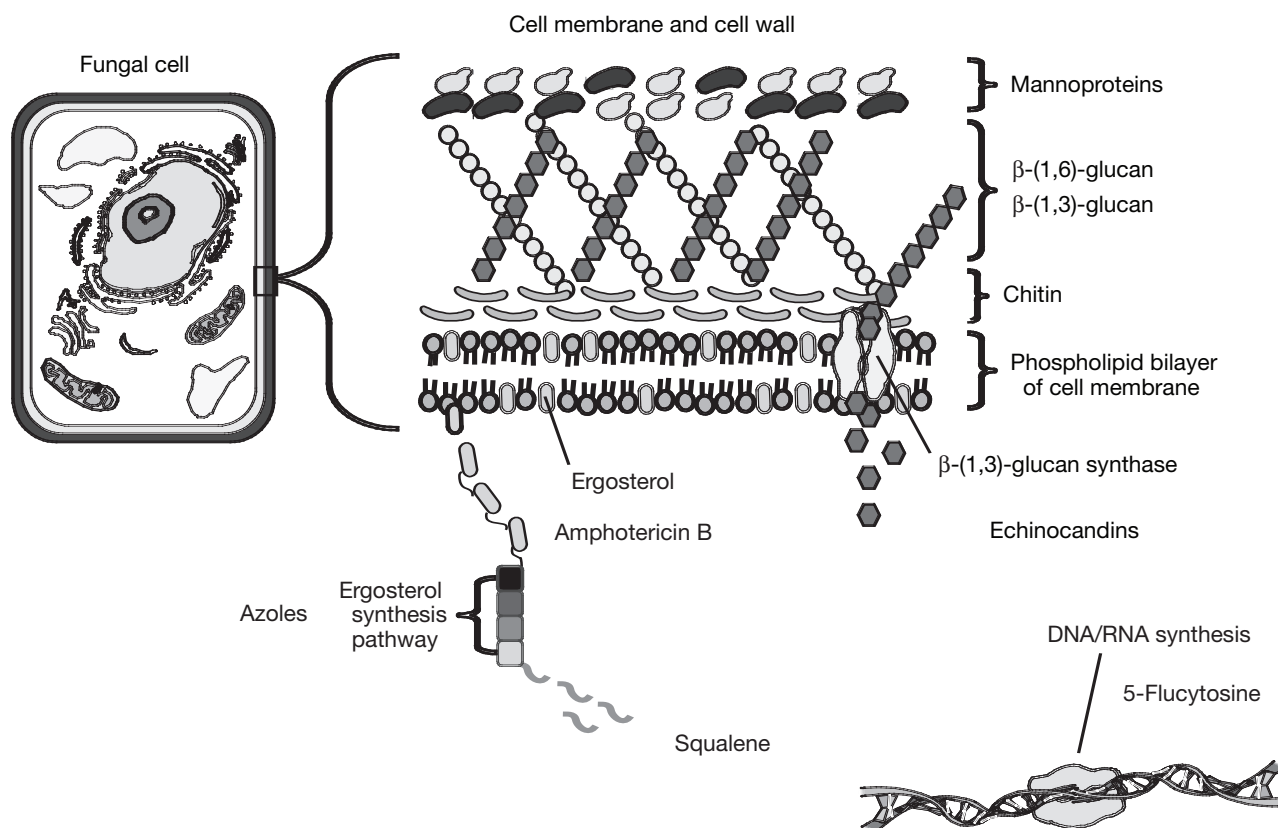


Figure 2. Antifungal drug targets. (Adapted from reference 33.)

in patients requiring long treatment durations (see Safety section). Both ABLC and L-AmB have been approved by the FDA for treatment of proven candidiasis as second-line therapy in patients who are intolerant of or refractory to AmBd. This treatment is supported by efficacy demonstrated in open-label studies.^{38, 44} In addition, the efficacy of ABLC was similar to that of AmBd in a randomized, multicenter trial involving patients with candidemia or invasive candidiasis; however, these results have not been published in the peer-reviewed literature.⁴⁵

Efficacy of ABLC in the management of invasive candidiasis was also reported in a study involving 979 patients from the Collaborative Exchange of Antifungal Research (CLEAR) registry, submitted by clinicians.⁴⁶ Patients received ABLC at doses ranging from 0.4–10 mg/kg/day; 30% of patients were cured, 30% improved, 16% had stable disease, and 24% deteriorated. Among patients with neutropenia, relatively poor outcomes were noted (only 24% cured or improved).

In a very small study of 66 adults with neutropenia and suspected or proven fungal infections, L-AmB was evaluated as therapy for invasive candidiasis.⁴⁷ Overall, L-AmB was associated with a higher rate of complete or partial response than AmBd after 14 days of therapy (46% vs 24%, $p=0.03$). However, results of the seven patients with confirmed candidiasis were not reported separately from the overall study cohort. Amphotericin B colloidal dispersion has also been successful in the management of invasive candidiasis. In an open-label, phase I study, escalating doses of ABCD (0.5–8.0 mg/kg, in increments of 0.5 mg/kg) were administered to HSCT recipients.⁴⁸ Of these patients, 53% of those with fungemia had complete response.

Efficacy of ABCD also was reported in a retrospective analysis involving 88 patients with candidiasis in five open-label studies.⁶ After receiving a median dose of ABCD 3.6 mg/kg/day for 72 days, 39 (58%) of 67 patients with candidemia had complete response. Five (7%) had partial response, and infection persisted or progressed in 23 (34%). The Infectious Diseases Society of America (IDSA) recommends 3–5 mg/kg/day when prescribing a lipid formulation of amphotericin B to treat invasive candidiasis.

Cryptococcal Meningitis

Several randomized trials have demonstrated that AmBd plus flucytosine is the gold standard

of induction therapy for cryptococcal meningitis in patients with and without HIV infection.^{49–52} In the first of these trials, a combination of AmBd plus flucytosine for 6 weeks was more efficacious than AmBd alone for 10 weeks.⁵⁰ Rates of cure and improvement were higher in the combination group versus the monotherapy group (67% vs 40%), rates of failure and relapse were lower (12.5% vs 41%), and sterilization of cerebral spinal fluid (CSF) was significantly more rapid.

A later study demonstrated that 6 rather than 4 weeks of treatment with AmBd plus flucytosine resulted in better overall response and fewer relapses, particularly among more severely immunocompromised patients or those with more complicated disease.⁵¹ In the mid-1990s, the availability of azoles with activity against *C. neoformans* prompted a study investigating an even shorter duration of induction therapy.⁵² For 2 weeks, patients with AIDS received AmBd 0.7 mg/kg/day plus either flucytosine 100 mg/kg/day or placebo, followed by azole maintenance therapy. After the 2-week treatment period, addition of flucytosine to AmBd was an independent predictor of negative CSF culture, but this did not result in improved outcomes overall.

Thus, the combination of AmBd and flucytosine is recommended by the IDSA as first-line therapy for patients with or without HIV infection who have cryptococcal meningitis.²² Alternatively, when AmBd cannot be tolerated, lipid formulations of amphotericin B may be substituted. One clinical trial compared L-AmB 4 mg/kg/day with AmBd 0.7 mg/kg/day as primary therapy for *C. neoformans* meningitis in 28 patients with HIV infection.³⁸ Liposomal amphotericin B was more effective than AmBd for CSF sterilization ($p<0.05$), but overall clinical response was similar with the two treatments. Therapy with ABLC 5 mg/kg/day demonstrated clinical efficacy in 18 (86%) of 21 patients with HIV-associated cryptococcal meningitis; however, CSF sterilization was not achieved for eight (44%) of the 18 patients after 6 weeks of treatment.⁵³

Invasive Aspergillosis

For decades, AmBd was the only available antifungal agent for the treatment of invasive aspergillosis.^{54–56} Most experts recommend high doses of AmBd (1–1.4 mg/kg/day) in this setting, with treatment duration depending on clinical, radiographic, and mycologic response to infection.⁵⁷ Since nephrotoxicity is often associated with AmBd at these high doses and

long treatment durations, lipid formulations of amphotericin B are another option. More recent studies have compared amphotericin B with newer agents such as voriconazole for the management of invasive aspergillosis.⁵⁸

Lipid formulations of amphotericin B have been studied in the management of invasive aspergillosis; most experience has been in patients with sinopulmonary disease and a few with disseminated or CNS infections. In a randomized, multicenter, European trial involving mainly patients with neutropenia and malignancies, L-AmB 1 and 4 mg/kg/day demonstrated efficacy.⁵⁹ Most patients (75% [67/89]) had probable invasive aspergillosis, and sinus disease commonly occurred in those with pulmonary disease (89% [77/87]). Complete or partial clinical response was observed in 26 (63%) of 41 and 22 (48%) of 46 patients receiving 1 and 4 mg/kg/day, respectively. However, when patients with proven aspergillosis were compared using subsequently established standardized definitions, those receiving L-AmB 4 mg/kg/day had better response rates than those receiving 1 mg/kg/day (58% vs 37%). No significant differences in survival were noted between the two L-AmB dosage groups in this study; at 6 months, overall mortality was 63%, attributable mortality 21%.

More recent evidence failed to demonstrate a significant difference in clinical response with L-AmB 10 versus 3 mg/kg for the first 14 days of treatment; however, the frequency of nephrotoxicity was higher in the 10-mg/kg group.⁶⁰ Of importance, this was the first study, to our knowledge, to administer a lipid amphotericin B product as primary treatment of aspergillosis using the contemporary definitions of proven and probable aspergillosis. The response rate was comparable to that reported with voriconazole in similar high-risk patients.

In a double-blind, randomized trial involving 174 patients, ABCD 6 mg/kg/day was compared with AmBd 1.0–1.5 mg/kg/day.⁶¹ Significantly fewer ABCD- than AmBd-treated patients had proven or probable invasive aspergillosis at study entry (58% and 72%, respectively). Evidence at baseline was insufficient to support the diagnosis in 11.4% of ABCD-treated and 3.5% of AmBd-treated patients. Among those with proven or probable disease who received more than 7 days of antifungal therapy, complete or partial response was observed in nine (18.0%) of 50 and 12 (22.6%) of 53 patients receiving ABCD and AmBd, respectively ($p=NS$).

As part of the CLEAR program, outcomes of

398 patients receiving ABLC for invasive aspergillosis were reported.⁶² In this cohort, most (71%) patients had disease limited to the lungs. Of 368 evaluable patients, 162 (44%) experienced cure or improvement, and 78 (21%) had stable disease.

Zygomycosis

Amphotericin B is one of the few antifungal agents with clinical activity against Zygomycetes; however, outcomes are generally poor in immunocompromised hosts. Dosage escalation has been considered for such patients, particularly when using a lipid formulation of amphotericin B. Nevertheless, no consensus on optimal dosing has been established. The availability of newer agents has enabled clinicians to use combination antifungal therapy approaches against Zygomycetes infections.

One review summarized experience with 929 zygomycosis infections reported in the English-language literature since 1885.²⁸ Lipid formulations of amphotericin B and AmBd were the most common therapies described, with 12% and 57% of patients receiving these agents, respectively. Of those patients, 69% and 61%, respectively, survived. Fifty-one percent of patients received both surgical intervention and antifungal chemotherapy, with 70% survival. Survival was only 50% in those who received only surgical debridement. Multivariate analysis indicated that antifungal therapy and surgery were each an independent predictor of survival.

Experience with ABLC treatment for Zygomycetes infections in 64 patients was reported.^{63,64} Patients received a median dose of ABLC 4.82 mg/kg/day (range 0.9–12.6 mg/kg/day) over 16 days. Sinus cavity (32 patients) and lung (22) were the most common sites of infection. Cure (eight patients [13%]) or improvement (25 [39%]) was observed in 33 patients (52%) overall. At the end of ABLC therapy, disease was stable in 13 (20%) of the 64 patients. Of 35 receiving ABLC as salvage therapy for refractory zygomycosis, 24 experienced cure, improvement, or stabilization of disease.

Endemic Mycoses

Amphotericin B and its lipid formulations have considerable activity against most endemic fungal pathogens *in vitro*. Treatment with these agents in the clinical setting is largely supported by experiential data and has been documented mainly by case series. Since few randomized trials have been conducted in this area, published

national guidelines are particularly relevant for establishing the role of polyenes to treat these infections.

Coccidioidomycosis. Use of polyenes for management of chronic pulmonary or disseminated coccidioidomycosis has been supplanted mainly by azoles such as fluconazole and itraconazole. Amphotericin B is now typically reserved for patients with hypoxia and/or respiratory failure, those with rapidly progressing coccidioidal infections, or women during pregnancy because azoles are teratogenic. Dosages are intravenous AmBd 0.5–1.5 mg/kg once/day or every other day, and intravenous lipid formulations of amphotericin B 2.0–5.0 mg/kg/day.⁶⁵

Use of polyenes for this indication has been documented mostly only in case reports and open-label studies.^{66, 67} Intrathecal AmBd at doses ranging from 0.1–1.5 mg, with doses increasing until intolerance develops, has been administered at intervals ranging from daily to weekly in certain patients with coccidioidal meningitis in addition to systemic therapy with fluconazole in the hope of increasing rapidity of clinical response.^{65, 68} Lipid formulations of amphotericin B 2–5 mg/kg/day are alternatives to AmBd for coccidioidomycosis, but data supporting administration of lipid formulations are limited to open-label experience.^{44, 63}

Blastomycosis. Polyenes are one of the available treatment options recommended by the IDSA for patients with blastomycosis, although, to our knowledge, no large comparative clinical trials with any amphotericin B formulation have been performed.⁶⁹ Amphotericin B deoxycholate is the preferred treatment for pulmonary disease, life-threatening disseminated non-CNS disease, and disseminated CNS blastomycosis. It is also recommended for immunocompromised or pregnant patients, and children with life-threatening or CNS blastomycosis. In several case series, AmBd therapy was associated with clinical cure rates of 70–91% in patients with blastomycosis, and relapse rates were low when AmBd was administered in cumulative doses greater than 1 g.^{70, 71} Generally, the dose of AmBd is 0.7–1 mg/kg/day for these indications, with a goal of administering a total of 1.5–2.5 g. For patients with CNS disease, the dose should be at least 2 g.⁶⁹ As an alternative to AmBd, lipid formulations of amphotericin B can be prescribed, but no comparative trials have evaluated them in patients with blastomycosis. A report of open-

label experience with ABLC in 14 patients with blastomycosis showed cure or improvement in nine patients (64%).⁶³

Histoplasmosis. Amphotericin B deoxycholate is recommended as initial therapy in the management of severe forms of histoplasmosis, including acute and chronic pulmonary disease, disseminated disease, CNS disease, and granulomatous mediastinitis. In several patients with chronic pulmonary histoplasmosis, AmBd was associated with response rates of 59–100%.^{72–76} If AmBd dosages as high as 0.7–1 mg/kg/day are not tolerated, reduction to 0.5–0.6 mg/kg/day or substitution with a lipid formulation can be considered.⁷⁷ After the initial induction period, usually 2 weeks, treatment for most patients can be changed to an azole or an extended-interval dose of a polyene (1–3 times/week) for the maintenance phase of therapy.

In 25 patients with histoplasmosis who received ABLC, cure or improvement was observed in 21 patients (84%).⁶³ A randomized, double-blind, multicenter trial comparing L-AmB with AmBd suggested that the lipid formulation is preferred as induction therapy for patients with moderate-to-severe AIDS-associated histoplasmosis.⁷⁸ Clinical success was achieved in 45 (88%) of 51 and 14 (64%) of 22 patients receiving L-AmB 3 mg/kg/day and AmBd 0.7 mg/kg/day, respectively, as induction therapy for 14 days. Significantly fewer deaths occurred in the L-AmB group (2% [1/53], due to *Staphylococcus aureus* infection) than in the AmBd group (13% [3/24], due to progression of histoplasmosis; $p=0.04$). In addition, L-AmB was better tolerated than AmBd regarding both nephrotoxicity and infusion-related toxicity.

Empiric Therapy of Invasive Fungal Infections in Patients with Neutropenic Fever

Amphotericin B and its lipid preparations have demonstrated efficacy in the empiric treatment of patients with fever and neutropenia. The first trial that established the role of antifungal agents for treatment of neutropenic fever was conducted in patients with persistent neutropenic fever despite 7 days of receiving broad-spectrum antibiotics.⁷⁹ The addition of AmBd to broad-spectrum antibiotic therapy in one group of patients was compared with continuation of antibacterials or discontinuation of antibacterials altogether in two other groups of patients. In

this landmark study, the addition of AmBd to broad-spectrum antibiotic therapy was associated with substantially reduced rates of infection and/or shock (11% [2/18 patients]) compared with broad-spectrum antibiotics alone (38% [6/16 patients]) or discontinuation of antibiotics altogether (56% [9/16 patients]). Another multicenter trial confirmed these findings in patients with persistent neutropenic fever despite 4 days of broad-spectrum antibiotic therapy.⁸⁰ The rate of treatment success, defined by absence of fever and infection, was 69% in those who received AmBd 0.6 mg/kg/day compared with 53% in those who did not receive AmBd ($p=0.09$).

The lipid formulations of amphotericin B have also been investigated as empiric antifungal therapy in patients with neutropenic fever despite broad-spectrum antibiotic therapy. In a large, double-blind, multicenter, randomized trial, L-AmB 3 mg/kg/day was compared with AmBd 0.6 mg/kg/day in 660 patients who had neutropenic fever for at least 5 days despite broad-spectrum antibiotic treatment.⁸¹ Using a composite end point including defervescence, survival, successful treatment of baseline infection, and absence of breakthrough invasive fungal infection or toxicity requiring treatment discontinuation, L-AmB and AmBd resulted in similar success rates of 50% (172/343 patients) and 49% (170/344 patients), respectively. However, L-AmB treatment was associated with fewer proven breakthrough fungal infections: 11 patients (3.2%) versus 27 patients (7.8%, $p=0.009$). In addition, tolerability of L-AmB versus AmBd was better with respect to infusion-related reactions such as fever (17% vs 44%) and chills or rigors (18% vs 54%).

Amphotericin B colloidal dispersion 4 mg/kg/day was compared with AmBd 0.8 mg/kg/day in a prospective, randomized, double-blind study involving 213 adults and children with neutropenia and 3 or more days of persistent fever despite broad-spectrum antibiotic therapy.⁸² Of 193 evaluable patients, treatment was successful in 49 (50%) of 98 and 41 (43.2%) of 95 patients who received ABCD and AmBd, respectively ($p=0.31$). Similar rates of documented or suspected breakthrough fungal infection were reported in 14 ABCD-treated patients (14.3%) and 14 AmBd-treated patients (14.7%). Mortality rates were similar in the two treatment groups, with 16 and 13 deaths in the ABCD and AmBd groups, respectively.

Efficacy of ABLC and L-AmB was comparable

in two randomized trials involving patients with neutropenic fever despite antibiotic therapy.^{83, 84} However, neither study was designed to evaluate the efficacy of these formulations but rather to primarily assess drug safety. In another study, efficacy of low-dose ABLC 1 mg/kg/day was comparable to AmBd 0.6 mg/kg/day in patients with febrile neutropenia, although the primary outcome in this study was toxicity rather than efficacy.⁸⁵

Safety

The most common adverse effects associated with systemic administration of polyenes are infusion-related reactions and renal toxicity. These can be particularly challenging to manage in critically ill patients with complex disease. The lipid formulations of amphotericin B are often favored in the clinical setting since they enable administration of higher doses of amphotericin B for extended durations, which is often necessary when treating patients with invasive fungal infections.³⁹

Infusion-Related Reactions

Infusion-related reactions with AmBd administration have been reported in 70–90% of patients receiving the drug systemically.⁸⁶ Fever, chills, and shaking are classic reactions, and gastrointestinal complaints (e.g., nausea, vomiting, abdominal discomfort) have also been reported. Bronchospasm, hypotension, thrombophlebitis, and cardiac arrhythmias are less common but more severe reactions that have been reported. Pretreatment with drugs such as acetaminophen, diphenhydramine, and meperidine have effectively reduced these reactions in many patients.^{87, 88} Corticosteroids have also been administered but are generally not favored in this setting due to their immunosuppressive effects. Infusion time and drug concentration have been suggested as a factor in these reactions, but considerable controversy still exists in this area.^{89–92}

Infusion-related reactions have also been reported with lipid formulations of amphotericin B, to various degrees for each formulation. In general, these reactions have occurred with similar or less frequency with L-AmB and ABLC than with AmBd.^{81, 84, 93} In a trial of lipid formulations of amphotericin B as empiric therapy in patients with persistent fever and neutropenia who received no pretreatment drugs, infusion-related reactions on day 1 of therapy occurred in 88.5% of patients receiving ABLC 5

mg/kg/day compared with 52.0% and 48.0% of those receiving L-AmB 3 mg/kg/day and 5 mg/kg/day, respectively ($p < 0.001$ for both comparisons).

In other studies, infusion-related reactions were reported more frequently in ABCD- than AmBd-treated patients.^{61, 82} Similar to these reactions with AmBd, pretreatment with analgesics, antihistamines, and/or corticosteroids may mitigate many of those that occur with lipid formulations of amphotericin B.⁹⁴ However, these reactions may be formulation specific because the same patient may have a reaction to one formulation but not another.

More rare infusion-related reactions include a triad of hypoxia, back pain, and chest pain that has been reported with L-AmB.^{95, 96} Hypertension has also been reported with infusions of AmBd and its lipid formulations.^{81, 97–99} Hypoxia, dyspnea, and respiratory distress have also occurred in patients receiving ABCD, at times requiring mechanical ventilation. Hypotension particularly may be a problem with the higher doses of ABCD (≥ 7.5 mg/kg/day).^{48, 100} Some trials with ABCD were prematurely discontinued due to unacceptable toxicity associated with this lipid formulation.¹⁰¹ For these reasons, formulations other than ABCD are preferred by most clinicians.³⁹

Nephrotoxicity

Nephrotoxicity is a dose-limiting effect with all polyenes, and renal effects have been reported in up to 80% of patients receiving AmBd.^{81, 102–105} The mechanism of polyene-induced nephrotoxicity is thought to be due to the direct interaction between the polyene and the epithelial cell membranes, resulting in tubular dysfunction, as well as vasoconstriction and subsequent reduction of renal blood flow.^{106, 107} Some authors have suggested that deoxycholate, the detergent used to solubilize amphotericin B in conventional AmBd formulations, exerts some tubular toxicity.¹⁰⁸ Identified factors that increase the risk of polyene-induced nephrotoxicity include concomitant or underlying diseases, concomitant nephrotoxin therapy, daily and cumulative doses of amphotericin B, and residence in an intensive or intermediate care unit.^{103, 105, 109–111}

Saline loading before AmBd administration has reduced the occurrence of associated nephrotoxicity.^{112–114} Aggressive fluid resuscitation has also been suggested, achieved by maintaining a state of euvolemia with daily diuresis of 4 L or more while administering large fluid volumes and maintaining a serum potassium level above 4

mEq/L.^{115, 116} A combination of rehydration and saline loading has also been used.¹¹⁷

Extending the infusion time for AmBd with continuous infusions also has been suggested to mitigate AmBd-associated nephrotoxicity.^{89, 118, 119} However, since polyenes exert concentration-dependent killing activity, considerable concern exists regarding this approach. In addition, this approach has not yet been demonstrated as efficacious in randomized trials involving a substantial number of patients with invasive fungal infections. Therefore, continuous infusions of AmBd should be administered only in the experimental setting.^{120–123}

All of the marketed lipid formulations of amphotericin B have demonstrated reduced rates of nephrotoxicity relative to AmBd.^{61, 78, 81, 84, 124–126} However, nephrotoxicity has been reported with lipid formulations in several double-blind, randomized, multicenter trials of empiric therapy in patients with persistent fever and neutropenia.^{81–84, 127, 128} In most of these trials, L-AmB was administered, and in 11.5–29.4% of patients, baseline serum creatinine concentrations doubled. One study directly compared L-AmB 3 mg/kg/day with AmBd 0.6 mg/kg/day as empiric therapy in patients with persistent fever.⁸¹ Results showed that a significantly lower frequency of baseline serum creatinine concentrations doubled with L-AmB than with AmBd (18.7% vs 33.7%, $p < 0.001$).

In another comparative trial, the safety of L-AmB 3 or 5 mg/kg/day was compared with that of ABLC 5 mg/kg/day in patients with persistent fever and neutropenia.⁸⁴ In this study, serum creatinine concentrations were double those at baseline in 29.4% and 25.9% of patients receiving LAmB 3 and 5 mg/kg/day, respectively, compared with 42% of those receiving ABLC. One single-center trial included patients with more diverse baseline conditions, including fever, pneumonia, sinusitis, cellulitis, and documented invasive fungal infection.⁸³ Drug therapy consisted of 3–5 mg/kg/day of ABLC or L-AmB depending on baseline infection status. Results showed no significant differences in increases of serum creatinine concentrations relative to baseline levels between ABLC and L-AmB; 33% of ABLC recipients and 19% of L-AmB recipients had serum creatinine concentrations 1.5–3 times baseline values ($p = 0.19$).

Nephrotoxicity associated with ABLC also has been reported. In a large, multicenter, retrospective study involving patients who received at least four doses of ABLC for suspected or proven

invasive fungal infection from 1996–2000, serum creatinine concentrations doubled from baseline in 13% of 3514 patients; 3% of these patients required dialysis.¹²⁵ In an analysis of risk based on underlying disease, doubling of baseline serum creatinine concentrations was highest in allogeneic HSCT recipients (17%), followed by patients with leukemia (16%), solid organ transplant recipients (11%), and autologous HSCT recipients (11%).

The high rates of nephrotoxicity reported in some clinical trials apparently are not replicated with routine administration of ABLC in some medical centers.¹²⁹ Amphotericin B colloidal dispersion has demonstrated similarly reduced rates of nephrotoxicity relative to AmBd in comparative trials involving patients with invasive aspergillosis or neutropenia. In patients with invasive aspergillosis, serum creatinine concentrations doubled from baseline in 12.5% and 38.4% of those receiving ABCD 6 mg/kg/day and AmBd 1–1.5 mg/kg/day, respectively.⁶¹

Of importance, the reduced frequency of nephrotoxicity with lipid formulations of amphotericin B compared with AmBd may be particularly impressive in patients receiving concomitant nephrotoxins. In one trial, for example, serum creatinine concentrations doubled in 45% of patients receiving AmBd compared with only 30% of those receiving L-AmB 3 mg/kg/day.⁸¹ In general, higher rates of nephrotoxicity have not been observed when lipid formulations of amphotericin B are administered at higher than standard doses.^{125, 130, 131} In a recent prospective clinical trial, however, the rate of nephrotoxicity was higher in patients who received L-AmB 10 mg/kg/day than in those who received L-AmB 3 mg/kg/day for the first 2 weeks of treatment for invasive mold infections.⁶⁰

Electrolyte Imbalances

Derangements in electrolytes, including hyperkalemia, hypokalemia, and hypomagnesemia, are common with administration of AmBd or its lipid formulations.^{132–135} This is thought to be related to increases in membrane permeability caused by amphotericin B, which allows leakage of potassium from the cell and retention of hydrogen ions.¹¹³ Magnesium resorption may also be reduced, resulting in subsequent hypomagnesemia.^{113, 136} Hypokalemia may be particularly pronounced in patients receiving sodium supplementation.^{137, 138} Hypokalemia and hypomagnesemia, often signs of continuing distal tubular toxicity, are observed before declines in glomerular

filtration are evident. Patients requiring extensive potassium supplementation while receiving amphotericin B are actually exhibiting signs of nephrotoxicity despite having a normal serum creatinine concentration at the time. Severe electrolyte imbalances should receive immediate attention since they may be the initial signs of nephrotoxicity and ultimately lead to life-threatening arrhythmias.

Azoles

The discovery of azole antifungals was a huge step in the fight against superficial and systemic fungal infections, given the safety, efficacy, and oral bioavailability of these agents. The azoles, characterized by core 5-member azole rings, are classified into two general classes: imidazoles, which contain two nitrogens, and triazoles, which have three nitrogens on the azole ring. Imidazoles are relegated primarily to topical treatment of mucosal and superficial fungal infections due to lack of enzyme specificity, leading to adverse effects when administered systemically. Ketoconazole, the only systemically administered imidazole, was the first oral azole antifungal approved by the FDA. Structural modifications of ketoconazole led to the development of the triazole antifungals, which exhibit improved specificity for fungal enzyme targets, enhanced potency, and an expanded spectrum of activity against a variety of yeasts and molds. Four FDA-approved triazole antifungals are available: fluconazole, itraconazole, voriconazole, and posaconazole.

Mechanism of Action

Like polyenes, azoles exert their antifungal action within the fungal cell membrane. However, azoles inhibit cytochrome P450 (CYP)–dependent 14- α -demethylase (CYP51), preventing conversion of lanosterol to ergosterol and resulting in accumulation of methylsterols, fungal cellular disruption, and inhibition of growth and cellular replication (Figure 2).^{33, 139} Differences in the affinity to 14- α -demethylase in *Candida* species among the currently available azoles result in differences in their in vitro potency. In addition, although agents such as itraconazole and voriconazole demonstrate fungistatic activity against *Candida* species, they exert fungicidal activity against *Aspergillus* species.¹⁴⁰ Unfortunately, inhibition of fungal ergosterol synthesis by triazoles results in cross-inhibition of some CYP-dependent enzymes in humans, which may

contribute to the toxicity profile and drug-interaction potential of azole antifungals.

Clinical Efficacy

Fluconazole

Esophageal Candidiasis. Fluconazole 100 mg/day was compared with ketoconazole 200 mg/day for treatment of esophageal candidiasis in 169 patients with AIDS.¹⁴¹ Therapy was continued for 2 weeks after symptom resolution, for a maximum of 8 weeks. At the end of treatment, fluconazole- and ketoconazole-treated patients had an endoscopic cure rate of 91% and 52%, respectively ($p<0.001$), and a clinical cure rate of 85% and 65%, respectively ($p=0.006$). Fluconazole was also compared with itraconazole capsules for treatment of esophageal candidiasis in 2213 patients with AIDS.¹⁴² Fluconazole was associated with higher overall endoscopic and clinical cure after 2 weeks of treatment. However, when fluconazole was compared with itraconazole oral solution, the overall clinical response to itraconazole was comparable to that of fluconazole (94% vs 91%, $p=NS$).¹⁴³

In patients with AIDS at risk for recurrent esophageal candidiasis, continuous fluconazole 200 mg 3 times/week was associated with fewer episodes of oropharyngeal and esophageal candidiasis than when an episodic approach was used.¹⁴⁴ With the episodic approach, each case was managed independently. However, the final *Candida* species isolate collected was resistant in 45% of patients receiving continuous fluconazole, compared with 36% ($p=0.11$) of those in the episodic treatment group.

Candidemia. Fluconazole has been compared with AmBd for treatment of candidemia and invasive candidiasis in patients with⁴² and without^{41, 43} neutropenia. Results of the trials conducted in patients without neutropenia demonstrated that fluconazole 400 mg/day and AmBd 0.5–0.7 mg/kg/day had similar clinical response and survival rates, but fewer fluconazole-treated patients experienced toxicity. Another study compared fluconazole 800 mg/day with the combination of fluconazole plus AmBd in patients without neutropenia.¹⁴⁵ Results suggested no antagonism between fluconazole and AmBd. A trend toward greater success was noted with combination therapy (69%) than with fluconazole plus placebo (57%), but the difference was not significant ($p=0.08$). The combination therapy also was associated with improved bloodstream

sterilization compared with fluconazole plus placebo (94% vs 83%, $p=0.02$). Thus, the IDSA recommends fluconazole for treatment of candidemia, but the drug should generally be relegated to patients without neutropenia who have not received previous fluconazole therapy.¹⁴⁶ The studies evaluated only fixed doses of fluconazole. However, obese patients are at an increased risk for suboptimal dosing, and the IDSA recommends fluconazole 6–12 mg/kg for this special population.^{6, 147}

Empiric Treatment of Invasive Fungal Infections in Patients with Febrile Neutropenia. The role of fluconazole in the empiric treatment of invasive fungal infections in patients with prolonged fever and neutropenia despite antibacterial therapy is less well defined than it is for treatment of candidemia. Overall, the lack of large, well-controlled, comparative studies limits the recommendation of fluconazole as a first-line agent in this patient population. Two comparative studies, of which one was randomized, and one noncomparative study involved patients with fever and neutropenia who received either fluconazole 400 mg/day or AmBd 0.3–1.2 mg/kg/day.^{45, 148, 149} Based on these limited data, fluconazole was as effective as and less toxic than AmBd. However, guidelines outline important concerns about using fluconazole as empiric therapy for febrile neutropenia.⁶ These concerns include the risk of colonization with fluconazole-resistant isolates or *Aspergillus* species when a patient has received prophylactic fluconazole, local patterns of fluconazole-resistant *Candida* isolates, and the clinical stability of the patient.

Prophylaxis Against Invasive Fungal Infections. Fluconazole has effectively prevented superficial and systemic fungal infections in patients with malignancies, including allogeneic HSCT recipients. In a randomized, double-blind, multicenter study involving patients who underwent bone marrow transplantation, fluconazole prophylaxis administered during the neutropenic phase was associated with reduced systemic and superficial fungal infections.¹⁵⁰ In the placebo group, 28 (15.8%) of 177 patients developed a systemic fungal infection compared with five (2.8%) of 179 in the fluconazole group ($p<0.001$). In another study, 31 (20%) of 152 patients receiving fluconazole prophylaxis in the first 75 days after bone marrow transplantation died compared with 52 (35%) of 148 patients receiving placebo ($p=0.004$).¹⁵¹ Recent guidelines

suggest fluconazole, among other antifungal agents, for prophylaxis in allogeneic HSCT recipients until engraftment, in patients with graft-versus-host disease requiring corticosteroids, and in those with acute leukemia receiving induction chemotherapy.¹⁵²

Fluconazole administered to prevent invasive candidiasis in intensive care patients is more controversial.¹⁵³ Factors associated with high risk of invasive candidiasis in intensive care patients include a higher score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, prolonged ICU stay, abdominal surgery, hemodialysis, broad-spectrum antibiotic therapy, placement of a central venous catheter, receipt of total parenteral nutrition, and corticosteroid therapy.⁹

Several trials have investigated the efficacy of prophylactic fluconazole in the ICU with mixed results.^{154–156} In a recent meta-analysis, fluconazole prophylaxis administered in intensive care patients was associated with fewer episodes of candidemia, but overall mortality was not affected.¹⁵⁷ Until further studies are conducted with a more generalized population of intensive care patients, routine administration of fluconazole for prevention of invasive fungal infections should be discouraged. Instead, fluconazole prophylaxis should be considered on a case-by-case basis in patients at highest risk.¹⁵⁸

Several studies have documented the utility of fluconazole prophylaxis for invasive fungal infections in liver transplant recipients, who are among those patients at highest risk of invasive fungal infection development. Fluconazole 100–400 mg/day has been compared with placebo and with other systemic and topical antifungal agents. Results have consistently demonstrated decreased fungal colonization, superficial fungal infections, and invasive candidiasis with fluconazole administration immediately after transplantation. However, fluconazole prophylaxis has not demonstrated decreased overall mortality in liver transplant recipients in these randomized controlled trials.

Therefore, fluconazole prophylaxis is recommended for liver transplant recipients who have the highest risk (i.e., two or more risk factors) of invasive fungal infection development immediately after transplantation.⁶ These risk factors include retransplantation, serum creatinine concentration above 2.0 mg/dl, choledochojejunostomy, intra-operative transfusion of 40 or more units of blood products, and fungal colonization detected within 2 days before and 3 days after transplantation.^{159, 160}

Cryptococcosis. Fluconazole is an important component in the management of cryptococcosis in patients with and without HIV infection. In a retrospective analysis of 83 patients without HIV infection, initial treatment with fluconazole was associated with a cure rate similar to that with AmBd.¹⁶¹ However, most patients with meningitis received AmBd initially. Randomized clinical trials involving patients without HIV infection who had cryptococcal meningitis are lacking; thus, recommendations for treatment in this population are the same as those for patients with HIV infection.²²

In a randomized, double-blind study of patients with AIDS and cryptococcal meningitis, AmBd 0.3 mg/kg/day was compared with fluconazole 200 mg/day.¹⁶² Overall success rates were similar between the AmBd- and fluconazole-treated patients (40% and 34%, respectively, $p=0.4$). However, relatively few patients in this study were at high risk of treatment failure (i.e., high cryptococcal CSF titers and opening pressures).

In another study involving patients with AIDS-associated cryptococcal meningitis, consolidation therapy with fluconazole 400 mg/day was compared with itraconazole 400 mg/day after 2 weeks of initial therapy with AmBd alone or combined with flucytosine.¹⁶³ In the consolidation phase, fluconazole therapy was associated with a higher rate of CSF sterilization than itraconazole (72% and 60%, respectively, $p=0.02$). In addition, secondary prophylaxis with fluconazole after initial clinical response was associated with fewer relapses and with prevention of recurrent cryptococcal disease. However, in patients with HIV infection who demonstrated sustained response to combination antiretroviral therapy ($CD4^+$ cell count > 100 cells/mm³), discontinuation of secondary prophylaxis with fluconazole can be considered.^{26, 164}

A clinical trial of AmBd plus fluconazole as induction therapy in patients with AIDS and cryptococcal meningitis has been completed.¹⁶⁵

Itraconazole

Esophageal Candidiasis. Itraconazole has been proven to be as effective as fluconazole for both oral and esophageal candidiasis in patients with AIDS.^{143, 166} Similar to the other indications for itraconazole therapy, the solution is the preferred oral formulation due to erratic absorption of the capsules.¹⁶⁷ In fact, the oral solution may be even more important for patients with esophageal candidiasis because a local effect may enhance

the systemic activity of itraconazole. Despite the success of itraconazole, its primary role is as a second-line agent for patients with fluconazole-refractory esophageal candidiasis. Itraconazole 200 mg/day has demonstrated reasonable success rates (44–65%) in patients whose fluconazole therapy failed.¹⁶⁸ Most of these data are from patients with advanced HIV disease. Other azoles, including voriconazole and posaconazole, as well as nonazole antifungals, have been effective alternatives in patients with fluconazole-refractory mucosal candidiasis.

Candidemia. Few trials have used itraconazole in the management of candidemia and invasive candidiasis. In a small study of 43 children younger than 10 years with candidemia, oral fluconazole 10 mg/kg/day was compared with oral itraconazole 10 mg/kg/day.¹⁶⁹ Overall cure was experienced in 82% and 81% of fluconazole- and itraconazole-treated patients, respectively. Due to the paucity of evidence and availability of other efficacious and safe agents, itraconazole is not recommended for treatment of candidemia.⁶

Aspergillosis. Early studies with itraconazole as primary treatment of invasive aspergillosis resulted in response rates similar to those with standard therapy.¹⁷⁰ In addition, response rates were similar in a subsequent open-label, non-comparative study in patients with pulmonary aspergillosis who received intravenous itraconazole for 2 weeks followed by capsules for 12 weeks.¹⁷¹ The poor absorption of the capsule formulation significantly reduced the utility of itraconazole in these patients. The oral solution and intravenous formulation have expanded the options for itraconazole administration and may result in more frequent achievement of therapeutic concentrations. However, clinical trials of the oral solution as primary treatment of invasive aspergillosis are limited, and, to our knowledge, no randomized, comparative trials have been performed. The success of voriconazole in this role has relegated itraconazole to a second-line agent in patients who are refractory to or intolerant of standard therapy for treatment of invasive aspergillosis.

Histoplasmosis and Blastomycosis. The availability of itraconazole revolutionized the treatment of blastomycosis and histoplasmosis. An open-label, multicenter, noncomparative, prospective trial evaluated itraconazole 200–400 mg/day to treat nonmeningeal, non-life-

threatening histoplasmosis or blastomycosis.¹⁷² Long-term treatment with itraconazole resulted in cure rates of 86–95% in this study. However, no comparative agent was used, nor were patients with severe, life-threatening infections included. Most clinicians agree that for patients with more severe disease, AmBd (or L-AmB for those with disseminated histoplasmosis) should remain the treatment of choice for induction therapy, with oral itraconazole solution for consolidation therapy once the patient's condition has stabilized.^{69, 78}

Empiric Treatment of Invasive Fungal Infections in Patients with Febrile Neutropenia. Itraconazole was evaluated as empiric treatment of fungal infections in 384 adults with neutropenia, hematologic malignancies, and persistent fever in an open-label, multicenter, randomized, non-inferiority study.¹⁷³ Patients were randomized to receive intravenous itraconazole followed by oral itraconazole solution or intravenous AmBd. Overall, 47% of patients in the intent-to-treat group receiving empiric itraconazole became afebrile compared with 38% of those receiving AmBd. No significant between-group difference was noted in the frequency of breakthrough fungal infections. Patients receiving itraconazole had significantly fewer drug-related toxicities than those receiving AmBd (5% vs 54%, $p=0.001$). The relatively low occurrence of adverse effects with itraconazole and the agent's ability to achieve adequate concentrations with oral administration in this high-risk population are attractive.

Based on these data, itraconazole oral solution was approved by the FDA for administration as empiric therapy in patients with fever, neutropenia, and suspected fungal infection. For these high-risk patients however, current guidelines recommend antifungal agents other than itraconazole (e.g., caspofungin or an amphotericin B formulation).^{152, 174}

Prophylaxis Against Invasive Fungal Infections. Itraconazole has been evaluated as prophylaxis for patients at high risk for invasive fungal infection development. High-risk patients include those with prolonged and severe neutropenia, such as recipients of an allogeneic stem cell transplant and patients receiving chemotherapy for acute leukemia. Several studies comparing oral or intravenous fluconazole with itraconazole suggest that itraconazole is associated with development of fewer invasive mold infections but more treatment-related

adverse effects.^{175, 176} The authors of a large meta-analysis evaluated randomized controlled trials of itraconazole for antifungal prophylaxis in patients with neutropenia and hematologic malignancies.¹⁷⁷ The analysis included 13 trials with over 3500 patients. In a dose-dependent fashion, itraconazole significantly reduced the rate of proven invasive fungal infection by 53% and the rate of fungal infection–related mortality by 35%. In addition, itraconazole reduced the risk of invasive aspergillosis significantly by 48%. Itraconazole was effective only with 400 mg/day of the oral solution or 200 mg/day of the intravenous solution. Therefore, the cyclodextrin vehicle is vital to the absorption and clinical utility of itraconazole.

In heart transplant recipients, itraconazole prophylaxis was identified as an independent protector for development of invasive aspergillosis (relative risk [RR] 0.2, 95% confidence interval [CI] 0.07–0.9, $p=0.03$) and prolonged 1-year survival (RR 0.5, 95% CI 0.3–0.8, $p=0.01$).¹⁷⁸ Itraconazole has been associated with higher discontinuation rates than fluconazole, presumably due to increased rates of nausea associated with cyclodextrin. In addition, itraconazole has been associated with hepatic toxicity and negative inotropic effects that can exacerbate or induce heart failure.

Therefore, when selecting antifungal prophylactic therapy for patients with malignancies, clinicians must carefully consider the following factors: toxicities associated with itraconazole, the potential of itraconazole to interact with chemotherapeutic agents, the availability of newer safe and effective antifungal agents, and the feasibility of therapeutic drug monitoring.¹⁵²

Voriconazole

With its relatively broad spectrum of activity and almost complete oral absorption, voriconazole is an attractive addition to the azole drug class. Voriconazole was FDA approved in 2002 and is indicated for treatment of invasive aspergillosis, candidemia in patients without neutropenia, esophageal candidiasis, and refractory infection due to *Scedosporium apiospermum* or *Fusarium* species.¹⁷⁹

Esophageal Candidiasis. Oral voriconazole 200 mg twice/day demonstrated noninferiority to oral fluconazole 200 mg once/day for treatment of esophageal candidiasis in patients with AIDS.¹⁸⁰ However, voriconazole is still considered an alternative therapy for treatment of esophageal

candidiasis. Its activity against resistant *Candida* species (especially *C. albicans*) provides potential for its administration in patients with mucocutaneous candidiasis that is refractory or resistant to fluconazole.¹⁸¹

Candidemia. Voriconazole was compared with AmBd as treatment for candidemia in patients without neutropenia. A multicenter, noninferiority trial compared intravenous voriconazole 6 mg/kg every 12 hours followed by 3 mg/kg every 12 hours with AmBd 0.7–1 mg/kg/day in 422 patients.¹⁸² Conversion to oral therapy was permitted after 3 days of intravenous administration; patients randomized to AmBd received fluconazole. Baseline characteristics of both groups were similar, including the 50–60% of patients infected with non-*albicans* species.

In both groups, 41% of patients demonstrated mycologic cure and clinical cure or improvement 12 weeks after completion of therapy (95% CI 10.6–10.6). At the last follow-up visit, clinical success was seen in 65% and 71% of voriconazole- and AmBd-treated patients, respectively, as determined by a blinded data review committee ($p=0.42$). Voriconazole performed as well as AmBd against infections due to non-*albicans* species; however, the results suggested a better response for voriconazole-treated patients with *C. tropicalis* infections, with 17 (32%) of 53 voriconazole-treated patients experiencing clinical success versus one (6%) of 16 AmBd-treated patients ($p=0.032$).

Invasive Aspergillosis. In a noncomparative study, voriconazole initially demonstrated promise of prophylaxis against *Aspergillus* infections as salvage or primary therapy in 116 patients with invasive aspergillosis.¹⁸³ Complete or partial response to therapy was demonstrated in 56 (48%) of 116 patients treated with voriconazole. Among the 60 patients receiving primary therapy, complete or partial response was achieved in 35 (58%). These results were comparable or slightly better than those noted with historical controls and prompted a large trial using voriconazole as the primary treatment of invasive aspergillosis. In this landmark, multinational, randomized, open-label trial, intravenous followed by oral voriconazole was compared with AmBd for at least 7 days followed by other licensed antifungal therapy.⁵⁸ Baseline characteristics of the 277 patients in the modified intent-to-treat population were similar between treatment groups; most had either acute leukemia or had undergone allogeneic stem cell transplan-

tation. Similar percentages (> 80%) of patients in both groups had pulmonary aspergillosis. Significantly more voriconazole- than AmBd-treated patients had definite aspergillosis (46.5% vs 30.8%, $p=0.01$). More AmBd- than voriconazole-treated patients were given other antifungal therapy: 107 (80%) of 133 patients versus 52 (36%) of 144 patients.

The 144 patients randomized to receive voriconazole had significantly better outcomes at 12 weeks; 53% had complete or partial response compared with 32% of those receiving AmBd or other antifungal therapy (difference 21.2%, 95% CI 10.4–32.9). In the modified intent-to-treat group, 70.8% of the voriconazole-treated group survived versus 57.9% of the amphotericin B group at 12 weeks ($p=0.02$). In patients with invasive aspergillosis, initial therapy with voriconazole was associated with improved clinical outcomes and survival with fewer adverse events compared with those receiving standard therapy with AmBd.

Empiric Treatment of Invasive Fungal Infections in Patients with Febrile Neutropenia. In a multicenter, randomized trial, voriconazole was compared with L-AmB in 837 patients who had primarily acute or relapsed leukemia or had undergone stem cell transplantation.¹²⁸ Fever and neutropenia had continued in these patients despite at least 5 days of antibacterial treatment. The primary end point in this study was success based on a composite of defervescence during the period of neutropenia, survival for 7 days after therapy, treatment of baseline infection, and absence of breakthrough invasive fungal infection or toxicity requiring treatment discontinuation. Patients were stratified based on previous antifungal prophylaxis and risk of fungal infection.

Overall response was 26% and 31% with voriconazole and L-AmB, respectively (95% CI 10.6–1.6), which did not meet the prespecified criteria to demonstrate noninferiority. The FDA therefore did not approve voriconazole for this indication. However, patients receiving voriconazole had fewer breakthrough fungal infections than those receiving L-AmB (1.9% vs 5%, $p=0.02$). Thus, voriconazole is considered an option by some clinicians and in national guidelines for empiric treatment of invasive fungal infection in patients with persistent neutropenic fever.¹⁵² However, with recent reports of breakthrough fungal infections, including those caused by Zygomycetes, continued surveillance and exploration is warranted in patients receiving

voriconazole prophylaxis.¹⁸⁴

Rare Fungal Infections. Voriconazole has demonstrated efficacy in the treatment of certain rare fungal infections due to *Penicillium*, *Fusarium*, and *Scedosporium* species.¹⁸⁵ In an open-label, noncomparative study, voriconazole was associated with a successful outcome in 90.0%, 45.5%, and 30.0% of patients with these infections, respectively. Often, these pathogens can be resistant to conventional antifungal agents and are becoming increasingly diagnosed in immunocompromised hosts.¹⁸⁶

Posaconazole

Posaconazole was approved by the FDA in September 2006 for prevention of invasive candidiasis and aspergillosis in severely immunocompromised patients at high risk for development of these infections. In addition, posaconazole has demonstrated potential utility in the management of patients with documented invasive fungal infections caused by *Candida* and *Aspergillus* species and Zygomycetes in open-label, noncomparative clinical trials and in some small comparative studies.

Although early pharmacokinetic studies revealed a long terminal half-life of posaconazole, suggesting daily dosing, absorption of the drug did not increase at doses above 800 mg/day in healthy volunteers or severely ill patients.¹⁸⁷ In healthy subjects, divided daily doses substantially increased posaconazole exposures. A daily dose of posaconazole 800 mg given as 400 mg twice/day provided the greatest posaconazole exposure in severely ill patients, and exposure was increased with concomitant administration of food or a nutritional supplement.¹⁸⁸ The limitations of drug absorption contributed to the evaluation of lower doses administered more frequently in the phase III clinical trials.

Oropharyngeal or Esophageal Candidiasis. In a randomized, multicenter, evaluator-blinded clinical trial, posaconazole suspension 200 mg/day was compared with a fluconazole 200-mg loading dose followed by 100 mg/day in 350 patients with HIV or AIDS and oropharyngeal candidiasis.¹⁸⁹ Overall success was similar with both treatments (91.7% and 92.5%, respectively). The mycologic success rate was higher with posaconazole than fluconazole (40.6% vs 26.4%, $p=0.38$). However, this did not appear to affect clinical relapse rates, which were also similar in both groups (31.5% vs 38.2%, $p=0.24$). The

trend toward higher mycologic persistence and clinical relapse rates with fluconazole did not appear to be due to the development of secondary resistance in *Candida* species.

Posaconazole was also evaluated in an open-label study involving 199 patients who had advanced HIV or AIDS and fluconazole-refractory oropharyngeal or esophageal candidiasis.¹⁹⁰ Oral posaconazole 400 mg twice/day for 3 days, then 400 once or twice/day for 25 days resulted in a clinical cure at 4 weeks in 85% of patients with refractory oropharyngeal disease and 72% of those with esophageal candidiasis.

Prophylaxis Against Invasive Fungal Infections in High-Risk Patients. Posaconazole was compared with fluconazole for prophylaxis against invasive fungal infections in patients with graft-versus-host disease after allogeneic bone marrow transplantation.¹⁹¹ In an international, randomized, double-blind study involving 600 patients, the overall frequency of breakthrough invasive fungal infection within 16 weeks of randomization was 5.3% and 9.0%, respectively, in posaconazole- and fluconazole-treated patients (odds ratio [OR] 0.56, 95% CI 0.30–1.07, $p=0.07$). This difference was driven by the overall rate of proven or probable aspergillosis in the posaconazole and fluconazole treatment groups (2.3% and 7%, respectively). The rate of breakthrough invasive candidiasis was not significantly different between the groups. Overall mortality rates in posaconazole- and fluconazole-treated patients were 25% and 28%, respectively.

In a multicenter study, patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome who developed fever and neutropenia were randomized to receive posaconazole oral suspension 200 mg 3 times/day, or fluconazole oral suspension 400 mg/day or itraconazole oral suspension 200 mg twice/day.¹⁹² Clinical outcome was determined by evaluators who were blinded to treatment assignments. Overall, posaconazole was associated with a lower rate of breakthrough fungal infection (2% vs 8%, 95% CI -9.7 to -2.5%, $p<0.001$). The rate of proven or probable breakthrough infections caused by *Aspergillus* species was lower in the posaconazole-treated patients (1% [2/304]) than in the fluconazole- or itraconazole-treated patients (7% [20/298]). However, rates of breakthrough infections caused by *Candida* species were similar between the groups.

Overall, posaconazole prophylaxis was associated with significantly longer survival than fluconazole or itraconazole ($p=0.04$) and with a 33% relative reduction in mortality rate. However, the probability of breakthrough infections with posaconazole therapy increased when plasma posaconazole concentrations fell below 710 ng/ml.¹⁹³ Therefore, monitoring posaconazole plasma concentrations may be warranted in certain high-risk populations due to the agent's unpredictable pharmacokinetic profile.

Empiric Treatment of Invasive Fungal Infections in Patients with Febrile Neutropenia. A multicenter, randomized, open-label study involving patients with refractory invasive fungal infections or febrile neutropenia investigated the pharmacokinetics, safety, and efficacy of three different dosing regimens of posaconazole.¹⁸⁸ In this study, 66 patients with febrile neutropenia were randomized to one of three treatment groups receiving different dosages of oral posaconazole. The greatest drug exposure was provided by posaconazole 400 mg twice/day. Successful clinical response was observed in 43% of patients with refractory invasive fungal infection and 77% of those with febrile neutropenia.

Salvage Therapy for Invasive Mold Infections. Posaconazole has been useful in patients who have refractory disease or cannot tolerate conventional antifungal therapy for aspergillosis, fusariosis, zygomycosis, coccidioidomycosis, and other rare mold infections.^{188, 194–198} In an open-label study of 32 patients with infections due to Zygomycetes, *Aspergillus* and *Fusarium* species, and other species refractory to standard therapy, nine (43%) of 21 patients with sufficient information to evaluate for efficacy had either complete or partial response to therapy.¹⁸⁸

One open-label, multicenter study using a historical control group evaluated posaconazole for treatment of invasive aspergillosis in patients who were refractory to or intolerant of conventional therapy.¹⁹⁹ An external data review committee determined that posaconazole was associated with an overall success rate of 42% compared with 26% in controls who were primarily receiving itraconazole and amphotericin B (OR 4.06, 95% CI 1.50–11.04, $p=0.006$). This study was conducted when voriconazole and echinocandins were not available. However, the findings suggest that posaconazole may be an alternative salvage therapy for patients with invasive aspergillosis and for those refractory to

or intolerant of initial antifungal therapy.

In a retrospective review of three separate studies evaluating posaconazole as salvage therapy for patients with invasive fusariosis, complete or partial response was demonstrated in 10 (48%) of 21 patients.¹⁹⁵ Hematologic malignancy was the most common risk factor for invasive fusariosis in 16 patients (76%); eight (38%) had neutropenia at baseline.

In another study, posaconazole 400 mg/day was administered as salvage therapy to 91 patients with proven or probable zygomycosis.¹⁹⁶ Patients were either refractory to (52%) or intolerant of (48%) other systemic antifungal therapy lasting 7 days or longer. Complete or partial response was demonstrated in 60% of patients; 21% had stable disease; 17% experienced treatment failure; and 2% had an undeterminable outcome. Thirty-five (38%) of the 91 patients died during therapy or within 1 month of discontinuation. Overall, despite the limitations of the retrospective study design, posaconazole resulted in relatively favorable outcomes for these difficult-to-manage patients.

Refractory Disseminated Coccidioidomycosis.

In one report, posaconazole was administered in six patients with disseminated coccidioidomycosis refractory to standard antifungal therapy.¹⁹⁸ Three of the six had acute, life-threatening disseminated coccidioidomycosis. Clinical signs and symptoms improved in all six patients, usually within 30 days of the start of posaconazole therapy. Five patients had successful outcomes after receiving posaconazole salvage therapy for 62–700 days.

Safety

Fluconazole

In contrast to the imidazole antifungals, fluconazole causes few severe adverse effects. In fact, doses of fluconazole have increased from 50 mg/day in initial clinical trials to 400–800 mg/day routinely used for invasive candidiasis.⁶ Most adverse effects experienced with fluconazole are minor (usually gastrointestinal) and rarely lead to discontinuation of therapy. However, fluconazole has been associated with some more severe adverse events, such as QTc-interval prolongation with torsades de pointes and elevations in hepatic transaminase levels, leading to rare cases of hepatic failure.^{200–202} These events typically occur in patients with underlying risk factors for the event.^{202, 203} Other adverse effects

include headache and, rarely, reversible alopecia. Due to reports of congenital abnormalities, fluconazole is a pregnancy category C agent, and the benefit to the mother should outweigh the possible risks to the fetus if administered during pregnancy.

Itraconazole

The safety of itraconazole is affected by the parent compound as well as the cyclodextrin vehicle. Adverse effects of the itraconazole solution, which contains a cyclodextrin carrier, include gastrointestinal effects (nausea, vomiting, diarrhea, and abdominal pain).¹⁶⁷ Gastrointestinal toxicity occurs more frequently with the oral than the intravenous solution.²⁰⁴ Other, less common adverse effects include rash, hypokalemia, headache, fever, and dizziness. Similar to other triazoles, itraconazole has been associated with hepatic toxicity ranging from mild, transient elevations of hepatic transaminase levels to rare cases of hepatic failure. As of March 2001, the FDA had received reports of 24 cases of liver failure in otherwise healthy patients and those with preexisting liver disease (including 11 deaths).²⁰⁵ Clinicians should monitor liver function tests especially in patients with preexisting liver disease.²⁰⁶

Itraconazole has safety characteristics that are typical of the triazole class but also has effects that are specific to the drug. In 2001 the FDA issued warnings after a review of serious adverse events revealed 58 cases of heart failure since the drug was first marketed in 1992.²⁰⁷ In approximately 45% of these cases, patients were taking itraconazole for treatment of onychomycosis, a relatively benign fungal infection. Itraconazole is thought to weaken the force of heart muscle contractions and is contraindicated for patients with heart failure. It is also relatively contraindicated for patients receiving concomitant therapy with negative inotropic agents or erythromycin. Thus, a black-box warning was added to the itraconazole prescribing information, and the drug should not be prescribed to treat onychomycosis in patients with ventricular dysfunction.

Another concern regarding intravenous itraconazole administration is the accumulation of the cyclodextrin vehicle in patients with renal insufficiency.²⁰⁸ Hydroxypropyl- β -cyclodextrin is excreted almost entirely unchanged in the urine. Aside from the gastrointestinal effects, cyclodextrin accumulation in rats has been associated with

pancreatic adenocarcinomas. The effect in humans is unknown, but intravenous itraconazole is contraindicated in patients with creatinine clearances less than 30 ml/minute.

Voriconazole

Distinctive adverse effects also occur with voriconazole. Photopsia, usually manifested as reversible alterations in color discrimination, blurred vision, the appearance of bright spots, and photophobia, occurs transiently in 20–30% of patients receiving voriconazole therapy.^{179, 185} Symptoms typically subside early in treatment (during the first week); however, patients should be advised to use caution when driving a motor vehicle during therapy. Investigations from phase II and III clinical trials predicted that the odds of a visual adverse event increase 4.7% for every 1- μ g/ml increase in voriconazole plasma concentration.²⁰⁹ The exact mechanism for this reaction is unknown, but reversible abnormalities in electroretinogram tracings are associated with these visual disturbances.

Asymptomatic elevations in serum transaminase levels have been observed in 12.4% of patients receiving voriconazole therapy and may be associated with higher plasma concentrations of the drug.¹⁷⁹ Rarely, patients may develop severe hepatitis. Therefore, appropriate monitoring of liver function tests before and during therapy is recommended.

In 7% of voriconazole-treated patients, skin rash has been reported, ranging from mild photosensitivity to severe reactions, including Stevens-Johnson syndrome. Visual hallucinations with no relation to photopsia have been reported in up to 4.3% of voriconazole-treated patients.¹²⁸ Again, the cyclodextrin vehicle (sulfobutylether- β -cyclodextrin) can accumulate in those with renal insufficiency and has been associated with formation of vacuoles in epithelial tissues of proximal renal tubules in rats.

Posaconazole

Adverse events were closely monitored through two phase II–III trials involving 428 patients treated with posaconazole for febrile neutropenia (66 patients) or refractory invasive fungal infection (362).²¹⁰ Overall, 164 patients (38%) reported an adverse event that was possibly or probably related to posaconazole. The most frequent treatment-related adverse event was gastrointestinal-related toxicity (nausea, vomiting, diarrhea, or abdominal pain). Gastrointestinal

events were also the most common reason for treatment discontinuation. Other treatment-related adverse events were elevated transaminase levels (3% of patients), altered drug levels (digitalis, cyclosporine, tacrolimus; 2%), QTc-interval and/or QT-interval prolongations (1%), and convulsions (< 0.5%).

Adverse events in these studies were compared in two treatment groups: short-term exposure (< 6 mo, 319 patients) and long-term exposure (\geq 6 mo, 109 patients). Findings suggested that adverse events seemed to depend on dose or exposure, occurring more often in patients with greater exposure to posaconazole 400 mg twice/day, but the difference was not significant. In addition, no significant differences were noted in rates of adverse events between the short- and long-term exposure groups.

Overall, posaconazole was well tolerated in a patient population with numerous comorbid conditions. Tolerability was documented in patients requiring extended treatment, which is important for those with serious invasive fungal infection. Direct comparisons with other triazoles were not performed in these phase II–III trials. However, posaconazole compared favorably with, or was better than, other triazoles, such as voriconazole, that may be administered for similar indications.

In a study comparing posaconazole with fluconazole to treat oropharyngeal candidiasis, treatment-related adverse events were similar in the two treatment groups.¹⁸⁹ Gastrointestinal toxicity was the most common adverse event in both groups.

Echinocandins

The echinocandins are the most recent antifungal drug class to be developed. The echinocandins are large lipopeptide molecules that contain an amphiphilic cyclic hexapeptide with an N-linked acyl lipid side chain.²¹¹ The differences in composition of the side chain make each echinocandin structurally unique. Caspofungin acetate is synthesized from a fermentation byproduct of the filamentous fungi *Glarea lozoyensis* and was the first echinocandin to be approved by the FDA.²¹² Initially, caspofungin was approved to treat invasive aspergillosis in patients refractory to or intolerant of other therapies. However, its efficacy has been demonstrated in patients with esophageal candidiasis, as empiric therapy in patients with neutropenia and fever, and as primary therapy in

those with candidemia.

Micafungin sodium is synthesized from a fermentation byproduct of the fungi *Coleophoma empetri* F-11899 and is FDA approved for treatment of esophageal candidiasis and for prophylaxis of *Candida* infections in HSCT recipients and treatment of patients with candidemia, acute disseminated candidiasis, and *Candida* peritonitis and abscesses.²¹³

Anidulafungin is synthesized from a fermentation byproduct of *Aspergillus nidulans*.²¹⁴ It is FDA approved for treatment of esophageal candidiasis, candidemia, and other forms of *Candida* infections, including intraabdominal abscess and peritonitis.

Mechanism of Action

The fungal cell wall is a rigid structure made of various glycoproteins, β -(1,3)-D-glucan, β -(1,6)-D-glucan, chitin, and galactomannan. The mechanism of action of the echinocandins is through the inhibition of the synthesis of β -(1,3)-D-glucan, an integral component of the fungal cell wall (Figure 2).²¹⁵ Decreased β -(1,3)-D-glucan production results in a weakened cell wall and loss of cell integrity, leading to lysis of the cell. The genes that encode the β -(1,3)-D-glucan synthase complex are *FKS1* and *FKS2*.²¹⁶ Transcription of fungal cell wall proteins regulated by *FKS2* is dependent on the enzyme calcineurin and the proteins regulated by *FKS1* regulated by fungal cell turnover.²¹¹

In *Saccharomyces cerevisiae*, a deletion in *FKS1* yields a phenotype that is hypersensitive to calcineurin inhibitors.²¹⁷ Deletion of both *FKS1* and *FKS2* genes is lethal, and mutations in *FKS1* confers caspofungin resistance. In addition, regulatory genes, such as *RHO1*, code for proteins involved in cell signaling and activation of a protein kinase cascade that affects synthesis of other necessary cell function processes.²¹⁸ The protein products of the genes coded by the *FKS* genes clearly are necessary for echinocandin activity. However, synthesis of β -(1,3)-D-glucan is complex, and the overall mechanism of action has not been fully elucidated.

Clinical Efficacy

Caspofungin

Esophageal Candidiasis. In a multicenter, double-blind, randomized trial involving primarily patients who were HIV positive, caspofungin 50 and 70 mg/day were compared

with AmBd 0.5 mg/kg/day to treat esophageal candidiasis.²¹⁹ Treatment was administered for 14 days. Response to therapy was determined by clinical resolution of symptoms and endoscopic clearing of lesions. A dose-related response to treatment was noted in the caspofungin-treated patients; 85% and 96%, respectively, achieved a favorable response at the end of therapy with 50 and 70 mg/day. The response rate in the 70-mg/day caspofungin group was significantly higher than that in the AmBd group. In a study involving patients with oropharyngeal and esophageal candidiasis, however, the dose-related response was more apparent between caspofungin 35 and 50 mg/day than between 50 and 70 mg/day.²²⁰ In addition, the overall response rate was higher in all caspofungin-treated patients than in those receiving AmBd.

Caspofungin 50 mg/day was compared with fluconazole 200 mg/day in 154 patients with advanced HIV (mean CD4⁺ count < 75 cells/mm³) and esophageal candidiasis.²²¹ Overall clinical response was 90% and 89% in the caspofungin- and fluconazole-treated patients, respectively; median time to symptom resolution was 4–5 days in both groups. However, 4 weeks after treatment, symptoms in 28% of caspofungin-treated patients recurred, compared with 17% of fluconazole-treated patients (difference 11%, 95% CI 5–29, $p=0.19$). Whether the higher relapse rate was due to antiretroviral failure in these patients is unclear, since caspofungin has demonstrated utility in the treatment of esophageal candidiasis in kidney transplant recipients.²²²

Candidemia. A caspofungin 70-mg loading dose followed by 50 mg/day was compared with AmBd 0.6–0.7 mg/kg/day in patients with invasive candidiasis and candidemia.²²³ Ten percent of the study patients had neutropenia (< 500 cells/mm³) and were given AmBd 0.7–1 mg/kg/day. In the intent-to-treat population, the overall response rate was 73.4% and 61.7%, respectively, in caspofungin- and AmBd-treated patients (adjusted difference 12.7, 95% CI 0.7–26.0, $p=0.09$). In the clinically evaluable patients, however, the difference between treatment groups increased to 15.4% (95% CI 1.1–29.7, $p=0.03$). In addition, no apparent difference was noted in clinical outcomes between caspofungin and AmBd groups when analyzed by *Candida* species; however, power to detect true differences in this subgroup analysis by pathogen was reduced because of the small sample sizes.

Aspergillosis. A caspofungin 70-mg loading dose followed by 50 mg/day was evaluated in a multicenter, open-label, noncomparative clinical trial involving 83 patients with proven or probable aspergillosis refractory to standard therapy. The pulmonary system was the most common site of infection (77.1% of patients). Response to therapy was determined by three expert medical mycologists based on information provided on the case report forms by the investigator. Of the 83 study patients, 80% were considered refractory to treatment, and 14.5% were considered intolerant of the initial therapy. Overall, 50% of patients with pulmonary aspergillosis responded to therapy. However, only 38% of the patients had proven disease; 26% of those with extrapulmonary disease had a favorable response. Overall, caspofungin demonstrated utility in the salvage treatment of invasive aspergillosis.

Nevertheless, the desire to improve outcomes of caspofungin-treated patients has resulted in the investigation of higher doses, and of caspofungin administration as part of a combination therapy for pulmonary aspergillosis. The utility of higher caspofungin doses has been complicated by an *in vitro* paradoxical regrowth of microorganisms at greater caspofungin concentrations; this suggests that increasing the doses for treatment of pulmonary aspergillosis may not be the optimal approach.^{121, 224}

A small, open-label study evaluated caspofungin combined with voriconazole in 47 patients with pulmonary aspergillosis whose amphotericin B therapy had failed.²²⁵ Study patients were randomized to receive voriconazole either alone or in combination with caspofungin. Those receiving the combination therapy had improved survival compared with those receiving voriconazole alone (hazard ratio 0.28, 95% CI 0.10–0.92, $p=0.01$). Whether this improved survival was due to the combination or to the caspofungin component of the treatment is unclear. Further studies with caspofungin clearly are needed to understand this agent's optimal place—either with higher doses or as part of a combination regimen—in the overall management of patients with pulmonary aspergillosis.

Empiric Treatment of Invasive Fungal Infections in Patients with Febrile Neutropenia. A caspofungin 70-mg loading dose followed by 50 mg/day and L-AmB 3 mg/kg/day were evaluated as empiric therapy in a randomized, multinational, double-blind study of patients with

fever ($> 38.0^{\circ}\text{C}$) and neutropenia (absolute neutrophil count < 500 cells/mm³ for 96 hours).¹²⁷ Study patients had primarily acute myelogenous leukemia, acute lymphocytic leukemia, and Hodgkin's lymphoma; 74% of patients had an absolute neutrophil count less than 100 cells/mm³. Primary outcome was an overall clinical response. Overall favorable response, determined by a blinded adjudication committee, was observed in 33.9% and 33.7% of the patients receiving caspofungin and L-AmB, respectively ($p=\text{NS}$). However, in those with a fungal infection identified at baseline, caspofungin was associated with higher rates of treatment success than L-AmB (51.9% vs 25.9%, $p=0.04$). Also, caspofungin was less likely than L-AmB to be discontinued prematurely due to toxicity (4.9% vs 8.2%, $p=0.02$). For empiric therapy in patients with fever and neutropenia, caspofungin was equally effective and better tolerated than L-AmB.

Micafungin

Esophageal Candidiasis. In a multicenter, randomized, double-blind study, micafungin 50, 100, or 150 mg/day was compared with fluconazole 200 mg/day in patients with HIV or AIDS, and esophageal candidiasis with or without oropharyngeal candidiasis.²²⁶ Endoscopic cure rates were 68.8%, 77.4%, and 89.8% with 50, 100, and 150 mg/day of micafungin, respectively, demonstrating a dose-related response. Overall efficacy of micafungin 100 and 150 mg/day was comparable to that of fluconazole; however, efficacy of micafungin 50 mg/day was inferior to fluconazole. After treatment, symptoms worsened in nine patients in the micafungin group compared with none in the fluconazole group.

Using data obtained from this study,²²⁶ investigators in a multicenter, randomized, double-blind study compared micafungin 150 mg/day and fluconazole 200 mg/day for 14 days to treat esophageal candidiasis.²²⁷ Overall endoscopic cure rate was 87.7% for micafungin and 88.0% for fluconazole at the end of treatment. Recurrence rate at the Week-4 visit was 15.2% and 11.3%, respectively, for micafungin- and fluconazole-treated patients ($p=0.257$). The investigators concluded that micafungin 150 mg/day is an effective treatment for esophageal candidiasis in patients with HIV or AIDS.

Candidemia. Micafungin was evaluated in an open-label, noncomparative study involving 126 patients with candidemia, either newly diagnosed

(72 patients) or refractory (54).²²⁸ Initial dose was micafungin 50 mg/day for patients with *C. albicans* and 100 mg/day for those with infections caused by other *Candida* species. The starting dose could be increased to as high as 200 mg/day based on overall clinical response. Patients with refractory disease could receive micafungin in addition to their current systemic antifungal therapy. Overall, 80% of patients received micafungin 100 mg/day or less. Complete or partial response was observed in 87.5% of patients with newly diagnosed candidemia and 76.0% of those with initial treatment failure who were receiving only micafungin. In patients with refractory disease who received micafungin in combination with another agent, the clinical success rate was 79.3%.

Micafungin 100 mg/day was compared with L-AmB 3 mg/kg/day in a multicenter, double-blind, international study involving patients with invasive candidiasis or candidemia.²²⁹ Of the 537 study patients, 55% were in the intensive care unit; however, only 12% had neutropenia. Mean APACHE II score was 15.7 ± 8.2 for all patients and was not significantly different between the two groups. Most infections were caused by non-*albicans* species, and approximately 16% had acute disseminated candidiasis. In the primary efficacy population, overall clinical and mycologic response at the end of therapy was 181 (89.6%) of 202 micafungin-treated patients and 170 (89.5%) of 190 L-AmB-treated patients. However, overall success at the end of treatment in the modified intent-to-treat groups was 183 (74.1%) of 247 patients in the micafungin group and 172 (69.6%) of 247 patients in the L-AmB group. No significant difference was noted in treatment success by species. Overall, micafungin demonstrated efficacy equal to that of L-AmB.

Micafungin 100 and 150 mg/day were compared with a caspofungin 70-mg loading dose followed by 50 mg/day in a phase III, double-blind, multicenter study involving primarily non-neutropenic patients with invasive candidiasis or candidemia.²³⁰ As in the previous study,²²⁹ overall mean APACHE II score was 14–15 and was not significantly different between groups. Approximately half the infections were caused by non-*albicans* species. Overall treatment success rates were 73.9% with micafungin 100 mg/day, 70.3% with micafungin 150 mg/day, and 71.4% with caspofungin ($p=NS$). However, in a post hoc subgroup analysis, efficacy was higher in patients infected with *C. glabrata* receiving micafungin 100 mg/day (85.7% [24/28 patients])

than in those receiving caspofungin (66.7% [22/33], $p=0.07$). In addition, 299 (77.9%) of 384 patients whose catheters were removed achieved treatment success compared with 91 (63.2%) of 144 whose catheters were not removed ($p=0.001$). Micafungin 100 mg/day provided outcomes similar to those with micafungin 150 mg/day and with standard doses of caspofungin; 100 mg/day appears to be the optimal micafungin dose for treatment of invasive candidiasis or candidemia.

Prophylaxis in Patients Undergoing Hematopoietic Stem Cell Transplantation. In a randomized, double-blind study, micafungin 50 mg/day was compared with fluconazole 400 mg/day in 882 patients undergoing either autologous or allogeneic HSCT.²³¹ Study drug was continued for a maximum of 42 days and was discontinued when absolute neutrophil count exceeded 500 cells/mm³. The overall rate of breakthrough infection was higher in the fluconazole versus micafungin group (26.5% vs 20.0%, $p=0.03$). These breakthrough infections included four cases of candidemia and one case of probable aspergillosis in the micafungin group, and two cases of candidemia and seven of aspergillosis (four proven, three probable) in the fluconazole group. Micafungin demonstrated efficacy superior to that of fluconazole as antifungal prophylaxis in HSCT recipients.

Aspergillosis. Micafungin was evaluated in an open-label, multicenter study in Japanese patients with deep-seated mycosis.²³² In this study, 42 (75%) of 56 evaluable patients had proven pulmonary aspergillosis, based on compatible symptoms, diagnostic imaging, and mycologic evidence. Patients were further categorized as those with pulmonary aspergilloma, invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis, and disseminated aspergillosis. Patients received micafungin 25–150 mg/day, and overall clinical response was determined by an independent expert medical review panel. Overall response rate was 57% (24/42 patients): 60% (6/10) with invasive pulmonary aspergillosis, 67% (6/9) with chronic necrotizing pulmonary aspergillosis, 55% (12/22) with pulmonary aspergilloma, and 0% (0/1) with disseminated aspergillosis.

In an open-label, noncomparative evaluation of micafungin alone or in combination with other antifungal agents, 225 patients with proven or probable invasive aspergillosis who were refractory to or intolerant of initial first-line

therapy were identified.²³³ In 191 patients (85%) whose initial therapy had failed, micafungin was added to their regimen. Overall, 80 patients (35.6%) demonstrated a favorable response as determined by a blinded adjudication committee. Response rates were higher in patients receiving micafungin as part of a combination regimen; however, only 34 (15%) of the 225 patients received micafungin monotherapy. Micafungin appears to be an effective treatment option for patients with pulmonary aspergillosis; further blinded comparative clinical trials are needed.

Anidulafungin

Esophageal Candidiasis. An anidulafungin 100-mg loading dose followed by 50 mg/day was compared with a fluconazole 200-mg loading dose followed by 100 mg/day for maintenance in a randomized, double-blind, clinical trial.²³⁴ This study involved 601 patients who were predominantly HIV positive and had esophageal candidiasis. Endoscopic resolution of lesions after 14–21 days of treatment was graded as either cured (complete resolution) or improved. The investigators also determined clinical response, defined as absence of or improvement in symptoms compared with baseline. At the end of treatment, endoscopic cure or improvement was noted in 97.2% and 98.8% of anidulafungin- and fluconazole-treated patients, respectively, and clinical response was noted in 98.8% and 99.6%. At 2-week follow-up, however, only 64.4% of patients had sustained endoscopic success with anidulafungin compared with 89.5% with fluconazole ($p < 0.001$). In addition, the lack of sustained response in more patients receiving anidulafungin versus fluconazole was complicated by more of the latter receiving antiretroviral drugs for their HIV.

Candidemia. An open-label evaluation of anidulafungin 50, 75, and 100 mg/day in patients with invasive candidiasis and candidemia reported overall clinical success rates of 84%, 90%, and 89%, respectively, at the end of treatment.²³⁵ In a phase III, randomized, double-blind study involving patients with candidemia and invasive candidiasis, an anidulafungin 200-mg loading dose followed by 100 mg/day was compared with a fluconazole 800-mg loading dose followed by 400 mg/day for 14 days after the last positive blood culture.²³⁶ Most (97%) patients in this study did not have neutropenia; 80% had APACHE II scores below 20, and the most common pathogen isolated at baseline was

C. albicans. At the end of treatment, overall clinical response was 75.6% with anidulafungin versus 60.2% with fluconazole (difference 15.4%, 95% CI 3.9–27.0, $p = 0.01$). This margin of improved efficacy with anidulafungin was maintained 2 weeks after completion of treatment. Overall mortality was higher in the fluconazole- versus anidulafungin-treated patients (31% vs 23%, $p = 0.13$).

Safety

Overall, the echinocandin class has a very favorable safety profile. In a collective safety evaluation of caspofungin clinical trials, the most common drug-related adverse events were fever (12–26%) and phlebitis at the infusion site (12–18%).²³⁷ In addition, the most common laboratory abnormalities were increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels, and decreased hemoglobin level and hematocrit; however, their frequencies were similar to those of the comparator drugs. Isolated cases of histamine-related symptoms with caspofungin have been reported only rarely.^{238, 239} Cases of hepatotoxicity have also been rarely reported in patients receiving caspofungin and cyclosporine concomitantly, but the overall contribution of caspofungin was uncertain.²⁴⁰ For patients who need to receive these agents concomitantly, the benefit of the drug should outweigh the risks, and liver function tests should be monitored.²¹²

Experience with micafungin and anidulafungin is less than with caspofungin. In clinical trials with patients receiving anidulafungin to treat candidemia, the most frequent adverse events were diarrhea (3.1%), hypokalemia (3.1%), and increased ALT level (2.3%).²³⁶ These findings were not significantly different from those seen with the comparator. Several reports of infusion-related toxicities have been reported, including hypotension and flushing, with anidulafungin.²³⁵ Although this effect may be related to the dehydrated alcohol used as a diluent in the formulation, the overall frequency of infusion-related reactions has been minimized by infusing anidulafungin at a maximum rate of 1.1 mg/minute.²¹⁴

In a dose-escalation study with 74 patients receiving micafungin up to 200 mg/day who were undergoing peripheral blood or stem cell transplantation, the most common adverse events were rash, headache, arthralgia, and hypophosphatemia.²⁴¹ In clinical trials with micafungin, the most common adverse events were nausea

(2.8%), vomiting (2.4), and increased AST, ALT, and alkaline phosphatase levels (2.7%, 2.6%, and 2.0%, respectively).²¹³

Extended experience with echinocandins is needed to appreciate any rare adverse events that might still occur; based on current evidence, however, the overall toxicity profile of the three available echinocandins is favorable.

Investigational Antifungal Drugs and Other Nonantifungal Agents

Monoclonal Antibody Against Heat Shock Protein 90

Human recombinant monoclonal antibody (MAB) against heat shock protein 90 (HSP90) is an intriguing potential addition to drug therapy for invasive *Candida* infections. A randomized, double-blind, multicenter trial evaluated administration of MAB HSP90 in combination with a lipid formulation of amphotericin B (either ABLC or L-AmB) versus a lipid formulation of amphotericin B alone for invasive candidiasis.²⁴² Results indicated that the addition of MAB HSP90 improved a variety of measured outcomes in the study patients. Complete overall response by day 10 of therapy was significantly higher with the combination therapy than with a lipid formulation of amphotericin B alone (84% vs 48%, $p < 0.002$). Of note, the reduction in mortality attributable to *Candida* by day 33 also favored combination therapy (18% vs 4%, $p = 0.025$). However, some concerns were raised regarding the study design and some of the definitions used.²⁴³ Preliminary data regarding administration of MAB HSP90 in combination with an echinocandin in animal models appear promising.²⁴⁴ This therapy represents a potentially significant advance in the management of invasive candidiasis. However, a confirmatory study would be beneficial, perhaps one involving this MAB in combination with an echinocandin.

Interferon- γ

Interferon- γ -1b demonstrates no inherent antifungal activity when given as a single agent but instead represents a way to improve the activity of effector cells of the immune system. This increased immune function potentially offers an addition to antifungal therapy for patients with compromised immune function due to disease states and their treatments, or to inherent defects in immunity. Both in vitro and in vivo, interferon- γ has upregulated the activity

of immune effector cells and led to dramatic increases in the antifungal activity of these cells across a variety of fungi.²⁴⁵ This increased activity leads to a dramatic increase in killing of both intracellular and extracellular fungi and is especially impressive when combined with antifungal agents. Furthermore, this increased antifungal activity of effector cells is not limited to only a few fungi but involves many pathogenic molds and yeasts.^{246–248} This therapy has been effective in case reports and small case series, but, to our knowledge, large clinical trials to demonstrate efficacy are lacking.^{249, 250}

Aminocandin

Structurally similar to the currently available echinocandins, aminocandin offers the advantage of a half-life that is 3–4 times that of other echinocandins.²⁵¹ This long half-life may permit administration as infrequently as once/week. The in vitro spectrum of aminocandin appears to be similar to that of other echinocandins in that it provides rapid and fungicidal activity against *Candida* species and inhibits *Aspergillus* species. Of interest is the apparent in vitro activity against some caspofungin-resistant strains of *C. glabrata*.²⁵² In animal models, aminocandin has demonstrated activity against *Candida* and *Aspergillus* species.^{253, 254} Aminocandin may have pharmacokinetic advantages over echinocandins. However, given the apparent similarity in spectrum to that of currently available compounds, the echinocandin market may not be perceived as large enough to continue development of this compound.

Ravuconazole

One of the new generation of broad-spectrum triazoles, ravuconazole is differentiated from posaconazole and voriconazole by its extended half-life (192 hrs in one study²⁵⁵). Besides its half-life, the in vitro activity of ravuconazole appears to offer little advantage compared with either posaconazole or voriconazole for treatment of yeasts or molds.^{256, 257} Healthy male volunteers achieved an initial peak serum drug concentration of 1052 ng/ml, which increased to 9133 ng/ml at day 29 of treatment with ravuconazole 400 mg/day.²⁵⁵ These concentrations are well above the MIC range observed with most *Candida* and *Aspergillus* species for ravuconazole. Unfortunately, ravuconazole 400 mg and 100 mg once/week were not effective in treating onychomycosis. However, ravuconazole 200 mg

Table 1. Qualitative Summary of Evidence to Support or Discourage Use of Antifungal Agents for Treatment of Invasive Fungal Infections

Infection	AmBd	ABCD	ABLC	LAmB	Flu	Itra	Vori	Posa	Caspo	Anidula	Mica
Candidemia	↑↑↑/↓	↑	↑↑↑	↑↑↑	↑↑↑	?	↑↑↑	?	↑↑↑	↑↑↑	↑↑↑
Esophageal candidiasis	↑↑↑	↑	↑	↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑/↓	↑↑↑/↓	↑↑↑
Cryptococcal meningitis	↑↑↑	?	↑	↑↑↑	↑↑↑	?	?	?	↓↓↓ ^a	↓↓↓ ^a	↓↓↓ ^a
Pulmonary aspergillosis	↑↑↑/↓	↑↑↑	↑↑↑	↑↑↑	?	↑	↑↑↑	↑	↑↑	?	↑
Empiric therapy for febrile neutropenia	↑↑↑/↓	↑↑↑	↑↑↑	↑↑↑	↑↑↑/↓	↑↑↑	↑↑	↑↑↑	↑↑↑	?	?
Prophylaxis of invasive fungal infections in high-risk patients	?	?	?	?	↑↑/↓	↑↑	↑↑	↑↑↑	?	?	↑↑↑
Zygomycosis	↑↑	?	↑	↑↑	↓↓↓ ^a	↓↓↓ ^a	↓↓↓ ^a	↑	↓↓↓ ^a	↓↓↓ ^a	↓↓↓ ^a

AmBd = amphotericin B deoxycholate; ABCD = amphotericin B colloidal dispersion; ABLC = amphotericin B lipid complex; LAmB = liposomal amphotericin B; Flu = fluconazole; Itra = itraconazole; Vori = voriconazole; Posa = posaconazole; Caspo = caspofungin; Anidula = anidulafungin; Mica = micafungin; ↑↑↑ = strong, ↑↑ = moderate, ↑ = weak evidence to support use; ? = inadequate data to support or discourage use; ↓ = weak, ↓↓ = moderate, ↓↓↓ = strong evidence to discourage use.

Levels of evidence were derived based on the number and quality of randomized controlled clinical trials. To assign a qualitative score, consideration was given if an active comparator was used, the study was open label, or a double-blind design was applied. In addition, indications in the prescribing information or product label and the toxicity profile (especially nephrotoxicity) were reviewed. When some evidence supported and other evidence discouraged the use of an agent in a clinical situation, this was generally a function of either a comparator agent with a more favorable toxicity profile or changing epidemiology that may limit use of the agent.

^aLack of microbiologic activity in vitro suggests poor clinical efficacy.

once/week was marginally effective.²⁵⁸ At the time of this writing, ravuconazole was undergoing phase I and II clinical trials.¹⁶⁵

Isavuconazole

BAL8557, a water-soluble prodrug of isavuconazole (BAL4815), is in phase III studies for its use as primary therapy of invasive aspergillosis and invasive candidiasis or candidemia. The water solubility of BAL8557 makes it unnecessary to administer the drug by a cyclodextrin carrier molecule. A study involving immunocompromised adults with esophageal candidiasis demonstrated outcomes with once-weekly BAL8557 administration comparable to those with fluconazole. The MICs for the infecting organisms were extremely low, ranging from 0.000125–0.008.²⁵⁹ With an intravenous loading dose of 200 mg of isavuconazole equivalents followed by 100 mg/day, isavuconazole maximum concentrations in healthy volunteers on days 1 and 14 of treatment were 2.32 and 2.55 µg/ml, respectively. The half-life of the drug in these patients was approximately 117 hours. With oral doses of BAL8557 identical to those described above, isavuconazole maximum concentrations were 1.85 µg/ml on day 1 and 2.61 µg/ml on day 14, with a half-life of 84.5 hours.²⁶⁰

To put these levels into perspective, in one study, BAL4815 had an isavuconazole MIC for 90% of the tested *Aspergillus* strains of 2.0 µg/ml or lower.²⁶¹ Isavuconazole's MICs were within one dilution of voriconazole's MICs for most *Candida* species, including those with decreased susceptibility to fluconazole.²⁶² Protein binding is approximately 95%, and dose-fractionation studies reveal that as with other azoles, the amount of time that the area under the curve of free drug concentration is above the MIC (AUC> MIC) appears to be the pharmacodynamic predictor of outcome with isavuconazole in *Candida* infections.²⁶³ Also, isavuconazole appears to have appreciable activity against Zygomycetes; none of the isolates tested had an MIC greater than 4.0 µg/ml, although only a few isolates have been reported thus far.^{264, 265}

In summary, isavuconazole appears to be an interesting broad-spectrum azole with very good oral bioavailability, an intravenous formulation devoid of cyclodextrin, and a spectrum of activity similar to that of posaconazole.

Other Azoles

Pramiconazole and albaconazole are broad-spectrum azoles in the early stages of development for treatment of onychomycosis dermatologic

fungal infections. However, the spectrum of these compounds may provide other options for management of invasive candidiasis, including disease caused by organisms resistant to other azoles.

Icofungipen

A compound with a novel mechanism of action, icofungipen is a cyclic β -amino acid with anti-*Candida* activity.²⁶⁶ The mechanism of action is distinct in that the compound appears to inhibit isoleucyl-transfer RNA synthetase, protein biosynthesis, and fungal cell growth.²⁶⁷ The spectrum of icofungipen is limited to *Candida* species and has been effective for treatment of disseminated candidiasis in neutropenic rabbits. However, it was less effective than fluconazole in humans with HIV and oropharyngeal candidiasis.^{267, 268}

Conclusion

Invasive fungal infections continue to occur at an ever-increasing rate in patients with HIV or AIDS, those with prolonged neutropenia, and those who are critically ill and in the ICU setting. The changing epidemiology of fungal pathogens combined with the variety of available drugs—which have different levels and quality of evidence, different toxicity profiles, and different drug-interaction potential—provides clinicians with numerous treatment options for invasive fungal infections (Table 1). The diagnosis and treatment of patients at risk for invasive fungal infection has improved but is still not optimal. The availability of several broad-spectrum triazole antifungals has given clinicians vital options for treatment of and prophylaxis against current and emerging fungal pathogens, such as *Candida* and *Aspergillus* species, and Zygomycetes. Evidence supporting administration of triazoles and echinocandins for prophylaxis and for empiric, primary, and salvage treatment of invasive fungal infection continues to grow.

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