# Newer Treatments for Fungal Infections

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**Abstract** Invasive fungal infections are a significant cause of morbidity and mortality among immunocompromised cancer patients, and until recently, treatment options have been limited. The poor outcomes of these infections, and the increased incidence of disease, particularly due to resistant and less common fungal isolates, necessitate the development of new agents. Antifungal drug development had been a slow process since the release of amphotericin B over 40 years ago. However, since 1995, six new systemic antifungals have been approved: three lipid formulations of amphotericin B, the initial second-generation triazole, and the first two approved agents in a new class of antifungals with a novel mechanism of action, the echinocandins. These newer agents, and several others currently in development, offer improved tolerability and safety profiles and extend the spectrum of coverage to resistant and less-common fungal infections. The authors describe each of these new compounds and discuss how they fit into the overall management of fungal infections in patients with cancer.

Invasive fungal infections have long been recognized as a significant cause of morbidity and mortality among immunocompromised patients. Over the past several years, coincident with more aggressive chemotherapeutic regimens and an increase in the number of patients with more prolonged severe neutropenia, we have witnessed an increase in, and changing epidemiology of, fungal infections in immunocompromised patients. Whereas *Candida albicans* and *Aspergillus* species continue to account for the majority of invasive fungal infections, there has been a recent increase in disease due to non-*albicans Candida* species (and antifungal-resistant *Candida* isolates) and less common molds, such as *Fusarium* species, the Zygomycetes and dematiaceous molds.[1–8]

Historically, the outcome of invasive fungal infections has been poor, and until recently, treatment options were limited. Amphotericin B deoxycholate (AmB), developed in the 1950s, had been the mainstay of therapy for decades. However, over the past several years, there have been unprecedented development and clinical use of antifungal agents. There are now three main classes of antifungal agents and others in development. Clinicians are able to choose among several agents with differing mechanisms of action, and are increasingly prescribing antifungal drugs in combination. This article will review these recent advances and discuss options for the treatment and prevention of invasive fungal infections in immunocompromised patients.

## Antifungal Drug Classes

There are three main classes of antifungals: polyenes (AmB and its lipid formulations) and azoles disrupt the cell membrane, and the recently developed echinocandins act on the fungal cell wall.

### COMPARISON OF AMPHOTERICIN B FORMULATIONS

Until recently, "conventional" AmB had been by default the only candidate for "gold standard" treatment of invasive fungal infections. Clinicians are well aware of the significant infusion-related effects (high fevers, shaking chills) and dose-limiting nephrotoxicity associated with AmB. In the 1980s, scientists utilized liposome technology for delivery of AmB and demonstrated both in the laboratory and in clinical studies that this formulation was much better tolerated, allowing for administration of larger doses than previously possible.[9]

There are currently three commercially available lipid formulations of AmB (Table 1). Dosage equivalency among the three lipid formulations of AmB has not been determined. All formulations allow for increased dosing of AmB with lower risk of nephrotoxicity.

In general, the lipid formulations are better

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tolerated than AmB. In a review of data available shortly after its approval, liposomal amphotericin B (L-AmB; AmBisome) appeared to be associated with a higher rate of clinical cure and less frequent infusion-related adverse events than the other two formulations.[10] In a recent study by Bowden et al,[11] infusion-related fever and chills were actually *more* frequent in patients treated with the lipid formulation amphotericin B colloidal dispersion (ABCD; Amphotec) than in those who received conventional amphotericin B. Wingard et al[12] evaluated the safety of L-AmB compared with amphotericin B lipid complex (ABLC; Abelcet) as empirical therapy in febrile neutropenia and found that L-AmB was associated with significantly less fever, chills, nephrotoxicity, and toxicity-related therapy discontinuation. Severe infusion-related events may be seen with any of the formulations, and tolerance of one product does not preclude the possibility of an adverse reaction to another.[13,14]

The improved tolerability of lipid formulations allows for increased dosing. Although the recommended adult dosing of L-AmB is 3–5 mg/kg intravenous (IV) daily, physicians have often increased the dose for patients whose infections do not respond to standard therapy. In a maximum tolerated dose study, Walsh et al[15] found that dosages of L-AmB as high as 15 mg/kg/day were effective and well tolerated.

### CHOICE OF LIPID FORMULATION OF AMPHOTERICIN B

For most clinicians in the United States, the choice of lipid formulation of AmB will be between the liposomal and lipid complex formulations, as use of the colloidal dispersion formulation has not been as widespread in this country. Some clinicians favor L-AmB because of reported experience of fewer toxicities associated with its use as compared with the use of ABLC[10,12] and because of published reports documenting the efficacy and tolerability of L-AmB at higher doses.[15,16] Many clinicians consider these agents comparable, and selection of an agent for hospital formularies may be based upon pharmacoeconomics. Although L-AmB compares favorably with other preparations, a major disadvantage is that it is the most costly (followed by ABLC and then ABCD) of these expensive alternatives to conventional AmB therapy. The cost per milligram for L-AmB is roughly tenfold higher than that for conventional AmB; thus, the daily cost for L-AmB is approximately *fifty* times that of AmB.

## Triazole Antifungals

Triazoles inhibit the cytochrome P450 enzyme 14α-demethylase, thus disrupting synthesis of ergosterol in the fungal cell membrane. Fluconazole (Diflucan) and itraconazole (Sporanox) are two triazoles approved in the 1990s and will not be discussed in detail in this review. Fluconazole is a widely used antifungal, and its increasing use as a prophylactic agent in immunocompromised patients at risk for fungal infection[17,18] has been correlated with an increased incidence of fluconazole-resistant organisms among this population.[19] Whereas fluconazole is only active against yeast, itraconazole has activity against filamentous fungi. Itraconazole is poorly absorbed after oral administration. The liquid form is preferred but often not well tolerated. An IV form of itraconazole has more recently become available. The newer second-generation triazoles have even broader coverage than itraconazole and in general appear to be better tolerated.

**Table 1**

Recommended Administration of Lipid Formulations of Amphotericin B

| FORMULATION | RECOMMENDED ADULT DOSE | INFUSION RATE |
|---|---|---|
| Amphotericin B lipid complex (ABLC) | 5 mg/kg/d | 2.5 mg/kg/hr (ie, over 2 hours) |
| Amphotericin B colloidal dispersion (ABCD, amphotericin B cholesteryl sulfate complex) | 3–4 mg/kg/d | 1 mg/kg/hr (ie, over 3–4 hours) |
| Liposomal amphotericin B (L-AmB) | 3–5 mg/kg/d | Infuse over 1–2 hours |

### VORICONAZOLE

Voriconazole (Vfend) is the first of the new broad-spectrum second-generation triazoles to be approved by the US Food and Drug Administration (FDA). It is the first antifungal agent since AmB to be licensed for first-line treatment of aspergillosis. The recommended dosing of voriconazole is as follows: for IV administration, 6 mg/kg every 12 hours for 2 doses, followed by 4 mg/kg every 12 hours; for oral administration, 200 mg every 12 hours for adults weighing ≥ 40 kg, and 100 mg every 12 hours for adults weighing < 40 kg. Because voriconazole is metabolized by the cytochrome P450 system, there are many potential drug interactions to consider. Concomitant use of voriconazole can lead to increases in levels of digoxin, warfarin, cyclosporine, tacrolimus (Prograf), and sirolimus (Rapamune), among others, and these patients should be monitored closely for toxicities. Isoniazid, rifampin, and phenytoin are among those drugs that can decrease levels of voriconazole.

The more common side effects seen with voriconazole include visual disturbances, dermatologic reactions, and elevated liver transaminase levels. Visual disturbances, including blurred vision, photophobia, and altered or enhanced visual perception, occurred in approximately 30% of subjects in clinical trials and in 45% in one recent study.[20] These reactions typically occurred within 30 minutes of drug administration and had a median duration of 30 minutes. The majority of these reactions are mild, rarely leading to discontinuation of the drug. In total, 6% of the subjects in clinical trials developed a rash. Photosensitivity rashes have been described, more often with long-term therapy, and patients taking voriconazole are advised to avoid direct sunlight. Increased liver transaminase levels were seen in 13% of subjects in clinical trials. Transaminase elevations are usually transient and may resolve without voriconazole adjustment. Doses should be adjusted for hepatic impairment. Dose adjustments for patients with renal insufficiency are not necessary for the oral formulation; however, administration of the IV form should be avoided in patients with moderate-to-severe renal impairment. Dose adjustment is not routinely indicated for patients on dialysis.

Voriconazole has enhanced activity compared with the first-generation azoles, with activity against *Scedosporium*[21] and *Fusarium* spp[22]; however, it is not active against the Zygomycetes. Perfect et al[23] recently reported results of a study of voriconazole for less-common or refractory fungal infections. The study showed a 50% satisfactory global response rate overall and 66% survival rate at 90 days.

Denning et al[24] reported a 48% response rate (complete or partial) with voriconazole treatment for acute aspergillosis and a 31% failure rate. Herbrecht et al[20] assessed voriconazole versus conventional AmB as initial therapy of invasive aspergillosis and reported improved survival and better response rates at 12 weeks and fewer side effects for the voriconazole group.

Although voriconazole is not approved as empirical therapy in febrile neutropenia, a study by Walsh et al[25] demonstrated fewer breakthrough fungal infections in patients who received voriconazole than in those who received conventional AmB for that indication. Voriconazole is also not approved for use in children, although data suggest it is well tolerated and effective in pediatric patients.[26]

### POSACONAZOLE

Posaconazole is an investigational triazole currently in phase III trials. Posaconazole has even broader coverage than voriconazole, with activity against the Zygomycetes.[27–29] Posaconazole is under investigation as an oral liquid form; there is no parenteral form as of yet. Absorption of the suspension is improved with divided daily dosing and high-fat meals.

### RAVUCONAZOLE

Ravuconazole is an oral triazole currently in phase II trials. It does not appear to have as broad a spectrum of coverage as voriconazole and posaconazole, with limited activity against the Zygomycetes, *Fusarium* spp, and *Pseudallescheria*. Potential advantages of this drug are high bioavailability and long half-life.[30]

## Echinocandins

The echinocandins represent the first new class of antifungals developed in decades. Echinocandins target the fungal cell wall, which has no counterpart in the mammalian cell; therefore, the echinocandins are predictably much better tolerated compared with existing antifungal agents. All are IV formulations and have the same general spectrum of activity. Echinocandins are not active against *Cryptococcus*, *Fusarium,* or Zygomycetes. Echinocandins have long half-lives, allowing for once-daily dosing.

### CASPOFUNGIN

In 2001, caspofungin (Cancidas) became the first echinocandin to be licensed in the United States. It has not been adequately studied as primary therapy for invasive aspergillosis. Caspofungin is administered as a 70 mg loading dose on day 1, followed by 50 mg daily maintenance therapy. The loading dose has not been evaluated for esophagitis, and dosing recommendations for that indication are to initiate therapy at 50 mg daily. Caspofungin is not approved for use in children, but pharmacokinetic studies in children indicate that initial proposed pediatric dosing of 1 mg/kg/day may be suboptimal and suggest that 50 mg/m$^2$/day may be appropriate dosing for children.[31] No dose adjustment is indicated for patients who have renal insufficiency or are on dialysis. Dose adjustment is recommended for patients with moderate hepatic insufficiency.

Caspofungin demonstrates activity against all *Candida* species and is highly active against most isolates. It is active in vitro against azole-resistant *Candida* spp and also to *C. lusitaniae*, which is typically resistant to AmB.[32] Caspofungin shows in vitro activity against *Trichosporon* spp, although a report described breakthrough trichosporonosis in a patient receiving caspofungin as prophylaxis against *Aspergillus.*[33]

Caspofungin is well tolerated and has few drug interactions. These factors and its activity against *Aspergillus* and azole-resistant and less-common *Candida* spp make it an attractive agent for use in immunocompromised oncology patients.

### MICAFUNGIN

Micafungin (Mycamine) is an echinocandin that is similar to caspofungin and was recently approved by the FDA. It is indicated for the treatment of esophageal candidiasis and as prophylaxis of *Candida* infections in stem-cell transplant patients. van Burik et al[34] reported the results of a randomized, double-blind trial of micafungin versus fluconazole as prophylaxis in stem-cell transplant patients. In that study, the overall success rate was significantly higher for those who received micafungin; fewer patients required empirical antifungal therapy, discontinued the drug due to adverse effect, or were diagnosed with aspergillosis. Micafungin has also been studied for the treatment of disseminated candidiasis and invasive aspergillosis. Ratanatharathorn et al[35] reported a 39% success rate for micafungin in combination with existing antifungal therapy for refractory aspergillosis in bone marrow transplant patients. Compared with previous reports citing success rates of less than 20% in these cases, these data suggest micafungin demonstrates added efficacy as part of combination therapy. Micafungin has a high therapeutic index and a half-life of approximately 13 hours, which could potentially allow for a less-than-daily dosing frequency.[36] The recommended doses of micafungin are 150 mg daily for treatment of esophageal candidiasis and 50 mg daily for prophylaxis of *Candida* infections in stem-cell transplant patients.

### ANIDULAFUNGIN

Anidulafungin is an echinocandin in clinical trials. It appears to have a similar spectrum of activity and safety profile compared with other echinocandins, although data are limited. Animal data indicate a large volume of distribution, suggesting extensive tissue distribution. The half-life is even longer than that of the other echinocandins, at approximately 30 hours.[37]

## Indications for Antifungal Therapy

These newer, well-tolerated antifungals are frequently used both in combination therapy and as prophylaxis for prevention of mold infections, although there are no data from randomized, controlled trials to support these uses. There is concern based upon in vitro data that some combinations of antifungal agents may act antagonistically together and thus may be less effective together than they would be separately.[38–40] Recent data with combinations of the newer antifungals suggest that these agents may act synergistically, but it must be emphasized that these data are the result of laboratory and retrospective outcome analysis and are not derived from controlled clinical trials to assess the safety and efficacy of combination antifungals.[40–42]

In addition to frequent "off-label" prescribing of antifungals, there are other concerns about widespread use of these agents. There have been recent reports of breakthrough mold infections in patients on long-term antifungal prophylaxis.[43,44] Emerging resistance resulting in a fungal infection refractory to all available drugs is a frighteningly real possibility. Healthcare organizations cannot ignore the economic impact of these expensive drugs. As always, we must be concerned about the safety and well-being of our patients and avoid unnecessary use of these drugs. These guidelines provide recommendations for judicious use of antifungals as part of prophylactic, empiric, or treatment regimens.

### ANTIFUNGAL PROPHYLAXIS

There is no national standard for antifungal prophylaxis for high-risk patients. Some subsets of immunocompromised patients (ie, patients with acute myeloid leukemia, relapsed acute lymphocytic leukemia, or stem-cell transplant recipients) are at higher risk than others for fungal infection. Fluconazole has demonstrated efficacy against *Candida* species,[17,18] and micafungin was recently approved for prophylaxis of *Candida* infections in stem-cell transplant patients, but there is no proven effective method based upon data from randomized, controlled trials for the prevention of *Aspergillus* or other mold infections. Nevertheless, given the high risk for fungal disease, we and many other physicians believe it is reasonable to provide antifungal prophylaxis to certain immunocompromised patients through their period of increased risk (Figure 1).

Although not approved for this indication, voriconazole has been increasingly used for prophylaxis at many institutions. Voriconazole is an attractive option because it is relatively well tolerated, and there is an oral formulation available. Voriconazole also has a broad spectrum of activity, and there is legitimate concern about prolonged use selecting for resistant organisms, such as Zygomycetes, as has recently been described.[43,44] Voriconazole also has a variety of drug interactions and must be held prior to starting chemotherapy known to be metabolized by the cytochrome P450 system. We recommend clinicians consult a clinical pharmacist for assistance in the management of these high-risk patients, who may require dosing alterations due to concomitant medications or hepatic or renal insufficiency.

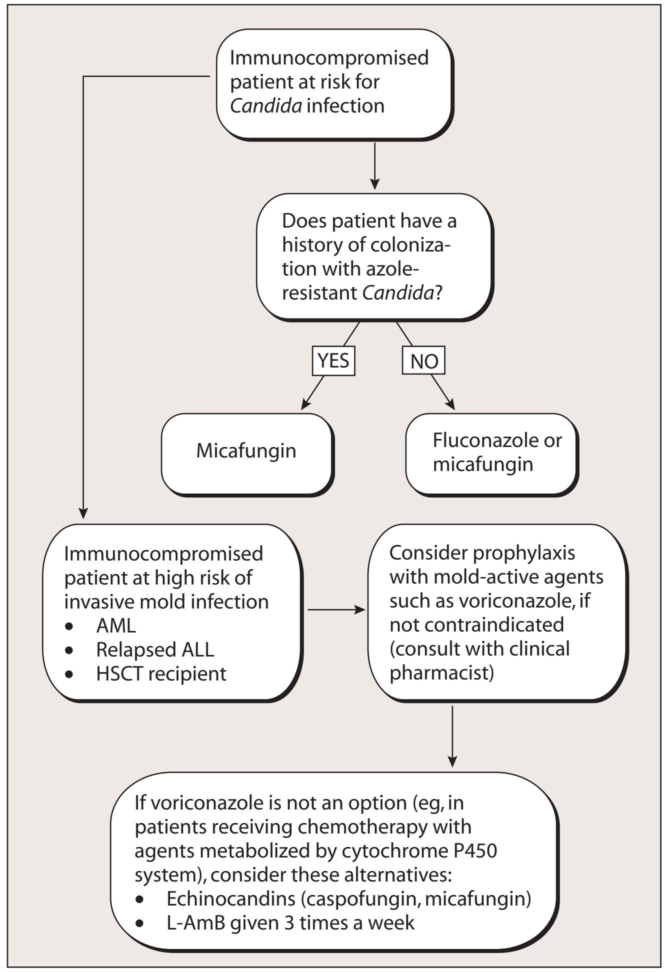


**Figure 1** Antifungal Prophylaxis

This treatment algorithm is for patients not requiring antifungal therapy for empiric use or for probable or proven infection.

Abbreviations: AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; HSCT = hematopoietic stem-cell transplant; L-AmB = liposomal amphotericin B

Other options for mold-active antifungal prophylaxis are less desirable, as they must be administered intravenously. The echinocandins are generally well tolerated, and many clinicians consider them as second-line options for patients unable to take voriconazole (eg, stem-cell transplant recipients and those receiving chemotherapy metabolized by the cytochrome P450 system). Because the echinocandins should be administered daily, many other clinicians favor L-AmB dosed three days a week. Although micafungin is approved for prophylaxis of *Candida* (and not mold) infections in stem-cell transplant patients, it is interesting to note that in the study reported by van Burik et al,[34] patients receiving micafungin prophylaxis also had fewer diagnoses of aspergillosis than those receiving fluconazole prophylaxis (one probable aspergillosis case in the

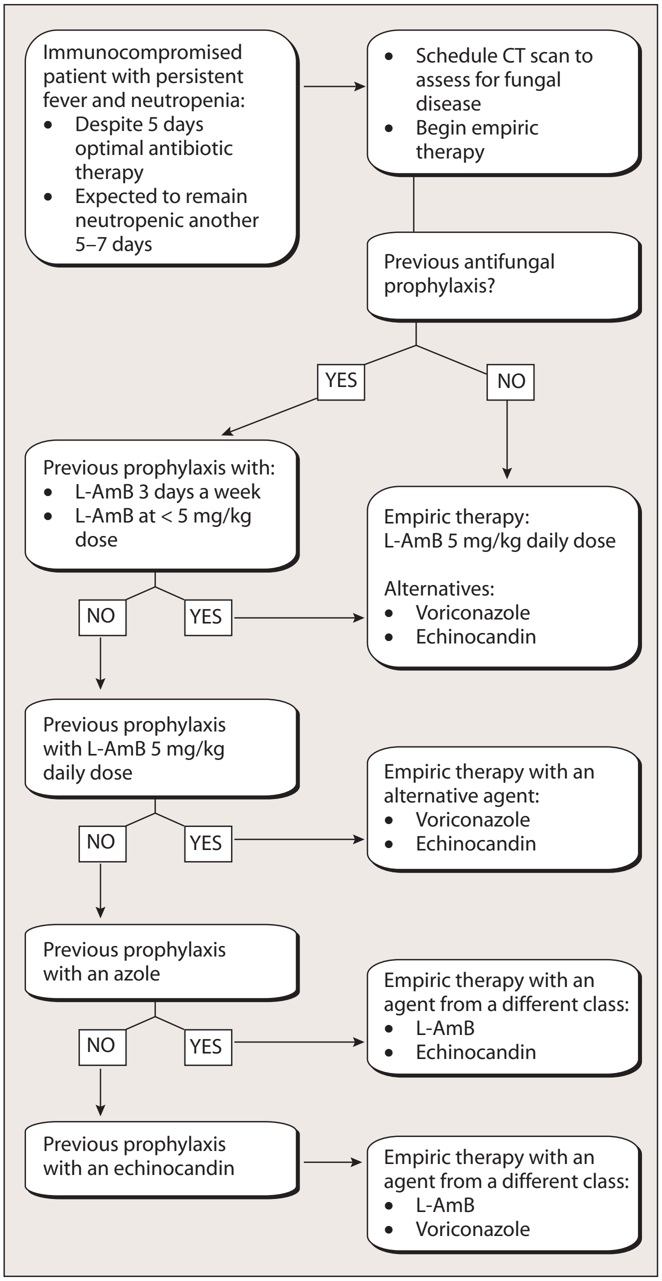


**Figure 2** Treatment Algorithm for Empiric Antifungal Therapy

Abbreviations: CT = computed tomography; L-AmB = liposomal amphotericin B

micafungin group vs four proven and three probable cases in the fluconazole group; $P = 0.071$).

### EMPIRIC USE OF ANTIFUNGALS

In accordance with accepted guidelines for management of the patient with febrile neutropenia,[45] we recommend initiating empiric antifungal therapy in any patient without an identified source of infection who has persistent fever and neutropenia for 5 days despite optimal antibiotic therapy and is expected to remain neutropenic for 5–7 more days. The usual drug of choice for empiric antifungal therapy is AmB or one of its lipid formulations administered daily. Although not approved for empiric treatment in febrile neutropenia, voriconazole or an echinocandin could be considered as reasonable alternative therapies.[25,46]

For patients who already have been receiving antifungal prophylaxis, we recommend discontinuing that agent and beginning therapy with a drug from a different class (eg, discontinuing voriconazole prophylaxis and beginning empiric L-AmB). For patients who have been receiving L-AmB at lower doses or less frequent intervals (eg, 5 mg/kg every Monday, Wednesday, Friday), it is acceptable to increase the dose of L-AmB to 5 mg/kg daily rather than switching to an alternate agent. In the absence of any evidence of probable or proven invasive fungal infection, there is no indication for empiric use of combination antifungal therapy (Figure 2).

## Treatment of Probable or Proven Invasive Fungal Infections

Although immunocompromised patients are susceptible to a wide variety of fungal pathogens, we will focus on treatment of candidal infections, invasive aspergillosis, and resistant molds that are significant emerging pathogens in this population.

### CANDIDAL INFECTIONS

Fluconazole has historically been effective for most *Candida* isolates, with the exception of *C. glabrata* (dose-dependent resistance) and *C. krusei* (intrinsic resistance). However, fluconazole-resistant *Candida* isolates have become increasingly common. Therefore, whereas most clinicians are comfortable initiating empiric treatment for esophageal candidiasis with fluconazole, many would favor another agent for initial treatment of a bloodstream infection. We would recommend empiric treatment with caspofungin or an AmB product in this instance, particularly for patients with previous azole therapy who are clinically unstable, who are known to be colonized with resistant isolates, or who are being treated in hospitals with high rates of fluconazole resistance. Although micafungin has been studied in disseminated candidiasis, it is not currently approved for the treatment of bloodstream infections. It is important to note that AmB resistance may be likely in isolates of *C. guilliermondii* and *C. lusitaniae*. Caspofungin may be active against some AmB-resistant isolates. Caspofungin, micafungin, or an AmB product should also be used for patients with esophagitis refractory to fluconazole treatment. Voriconazole has lower minimum inhibitory concentrations than fluconazole for most *Candida* spp and has activity against some fluconazole-resistant strains (Figure 3).

### INVASIVE ASPERGILLOSIS

Fluconazole should never be used for therapy of suspected, probable, or proven aspergillosis, as it has no activity against *Aspergillus* spp or other molds (Figure 4). Amphotericin B has by default been the standard of care for decades, although most clinicians would now consider voriconazole to be the

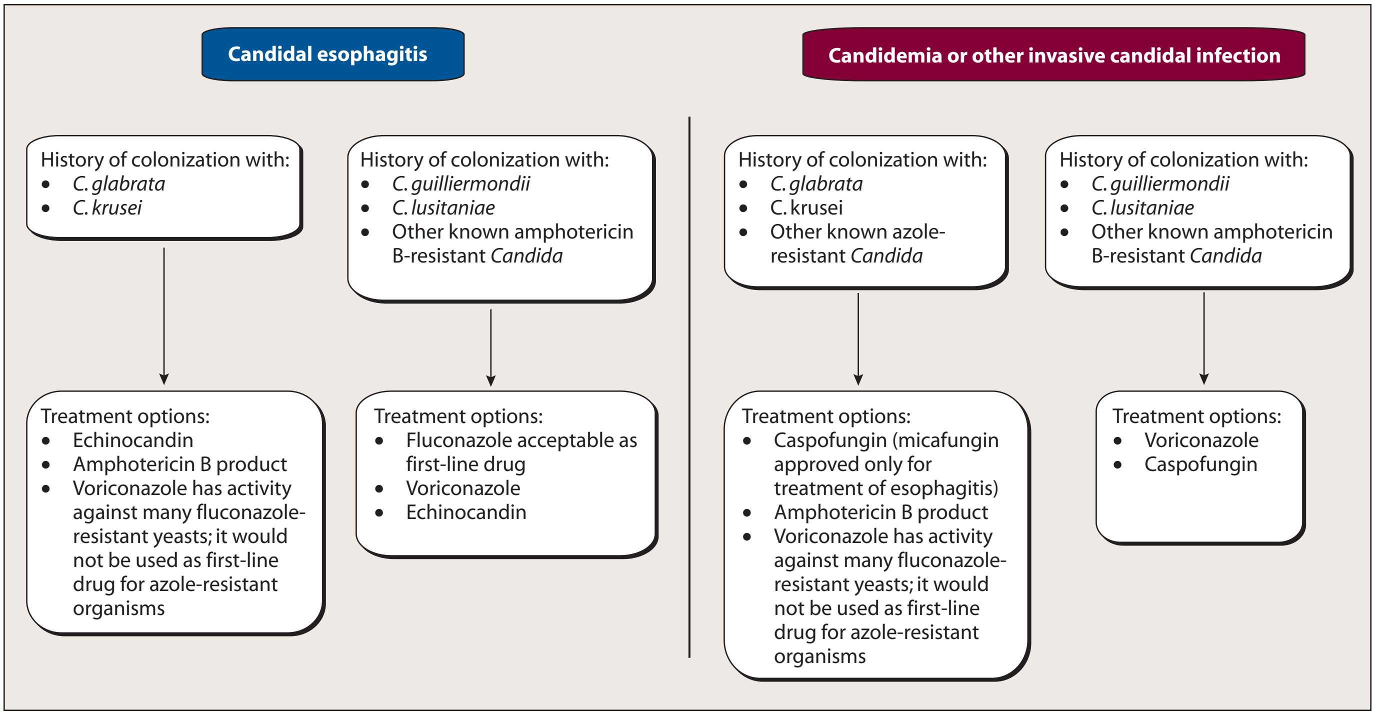


**Figure 3** Treatment Algorithm for Candidal Infection

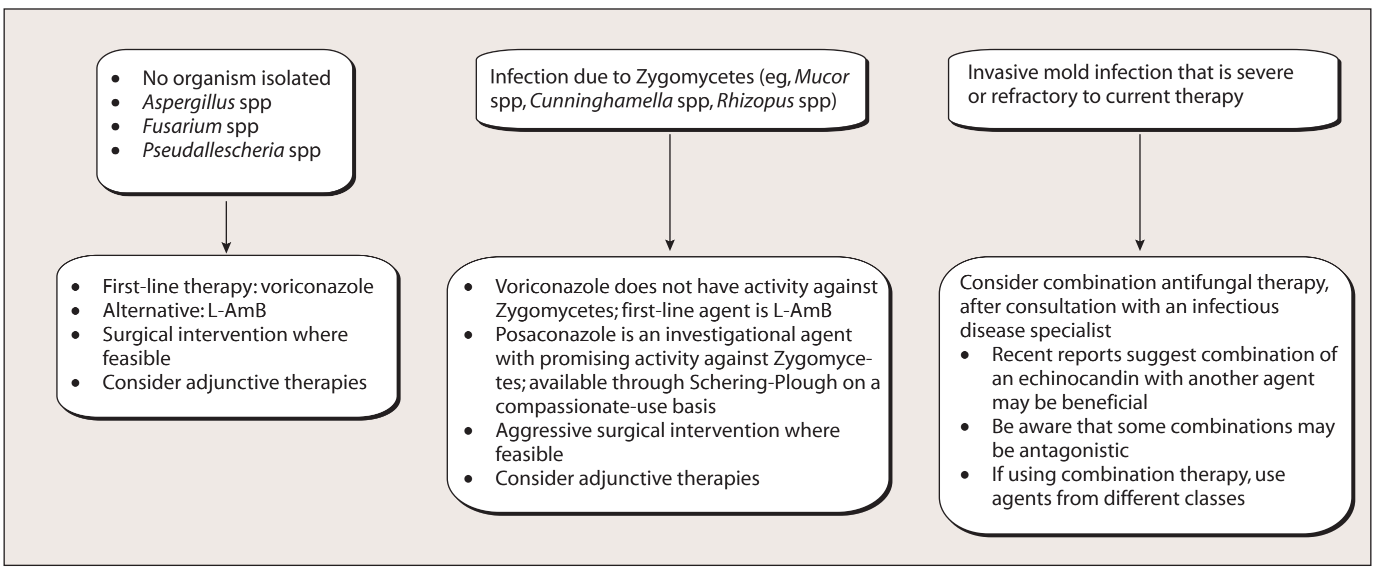


**Figure 4** Treatment Algorithm for Probable or Proven Invasive Mold Infection

Abbreviation: L-AmB = liposomal amphotericin B

agent of choice for first-line treatment of invasive aspergillosis. Voriconazole is fungicidal for *Aspergillus*, and is the first agent to be shown to have a survival advantage over conventional AmB for treatment of invasive disease.[20] Voriconazole is the treatment of choice for infections due to *Aspergillus terreus*, as these isolates are frequently resistant to AmB. In one in vitro study of clinical isolates, only 2% of isolates were susceptible to AmB, but 100% were susceptible to voriconazole.[47]

Given the prolonged course of therapy required and the significant risk of nephrotoxicity, most clinicians would favor using a lipid formulation if an AmB product is used. The economic impact of a course of lipid formulation of AmB must be weighed against the cost of prolonged medical care for acute renal insufficiency seen in a significant portion of those patients receiving conventional therapy.[48,49]

Caspofungin is fungistatic and not approved for first-line treatment of invasive aspergillosis. Its use should be reserved for patients intolerant of, or whose infections are refractory to, treatment with AmB products and voriconazole. Micafungin has been studied in invasive aspergillosis but does not currently have an approved indication for its treatment. Additionally, treatment with echinocandins may play a role in combination therapy, as discussed below.

### OTHER MOLDS

Coincident with increased numbers of severely immunocompromised patients and more widespread antifungal use, many centers are reporting the emergence of less-common molds, such as the Zygomycetes and the filamentous fungi *Fusarium* spp and *Pseudallescheria boydii*.[3–6]

Voriconazole has a broad spectrum of activity, including coverage of *Fusarium* spp and *Pseudallescheria boydii*, for which AmB has variable activity, and echinocandins are not effective.

However, voriconazole is not active against the Zygomycetes (including *Mucor* spp, *Rhizopus* spp, *Rhizomucor* spp, *Cunninghamella* spp, and *Absidia* spp). Zygomycoses are variably responsive to AmB, but none of the other currently commercially available drugs has activity against the Zygomycetes. Zygomycoses should be treated aggressively with maximum tolerated doses of AmB (ie, up to 10–15 mg/kg of L-AmB) and with surgical resection where feasible. These infections are difficult to treat and historically have been near universally fatal. However, more effective treatment may be on the horizon. Posaconazole is an investigational triazole that exhibits activity against the Zygomycetes.[27–29] Posaconazole may be obtained on a "compassionate-use" basis through Schering-Plough Research Institute (Figure 4).

### COMBINATION THERAPY FOR INVASIVE ASPERGILLOSIS

As previously stated, although use of combination antifungal therapy has become widespread, there is no published evidence supporting this practice. There are very little data about combination or sequential antifungal therapy, and results of various studies range from those demonstrating antagonism to those showing synergistic effects of antifungal combinations. Steinbach et al[40] reviewed reports published from 1966 to 2001 and abstracts from recent scientific meetings of in vitro, in vivo, and clinical responses to combination or sequential antifungal therapy for invasive aspergillosis. They found that in vitro combination reports showed higher percentages of synergistic (36% vs 14%) and additive (24% vs 20%) effects and lower percentages of indifferent (28% vs 51%) or antagonistic (11% vs 14%) effects than the in vivo combination reports. Data from this review suggest that echinocandins may show promise as part of combination antifungal regimens.

More recent studies have also shown a potential role for echinocandins in combination therapy. Petraitis et al[41] demonstrated in vitro synergistic interaction between the experimental agents ravuconazole and micafungin, associated with significant reductions in mortality in an experimental rabbit model of invasive pulmonary aspergillosis. Marr et al[42] reported that the combination of voriconazole and caspofungin was associated with an improved 3-month survival rate when compared with voriconazole alone when both regimens were used as "salvage" therapy in patients who had failure of initial AmB product therapy. These studies support further investigation of optimal use of combination therapy.

Combination antifungal therapy is frequently used at our institution, and we are aware that this is an increasingly common practice at many centers. Many clinicians favor using agents from two antifungal classes, and in some instances, drugs from all three major classes are used. Given what we know about optimal treatment of other conditions such as tuberculosis, malignancies, and HIV, it is intuitive reasoning to think that a combination of antifungals with differing mechanisms of action would be the best option for treatment of invasive fungal infections. Whether this is the case, or whether three drugs are better than two, remains to be seen. Our experience to date mostly has been with combination therapy used as a salvage regimen. If combination therapy is effective, it may be that it would be most beneficial if used as front-line therapy. Until data are available to address these many unanswered questions, we believe it is reasonable to advocate combination therapy of two or three agents for patients with severe or refractory invasive fungal infection (Figure 4).

## Summary

This is an exciting time in the field of medical mycology, with an unprecedented development of new agents, and new classes of agents, to combat invasive fungal infections in the immunocompromised host (Table 2). The echinocandins have excellent activity against resistant *Candida* spp and against *Aspergillus* spp. The second-generation triazoles have even broader activity, including *Fusarium* spp, and for posaconazole, promising results against the near universally fatal zygomycoses have been reported. There are many questions remaining to be answered regarding optimal management of invasive fungal infections, particularly related to use of combination antifungals and/or immunomodulating agents as adjunctive therapy. As more agents continue to become available in the coming years, clinicians will be faced with the novel challenge of selecting from among several viable options for antifungal therapy.

*A peer viewpoint on this article by Drs. Patrick McLeroth and Bruce Polsky appears on page 299.*

**Table 2**

Summary Table of Newer Antifungal Agents

| ANTIFUNGAL CLASS AND AGENT | RECOMMENDED DOSING | APPROVED INDICATIONS | SPECTRUM OF ACTIVITY | RESISTANCE OBSERVED | OTHER COMMENTS |
|---|---|---|---|---|---|
| **Polyenes** | | | | | |
| Amphotericin B lipid complex | 5 mg/kg IV qd; infuse at 2.5 mg/kg/hr | Invasive fungal infections in patients refractory to or intolerant of AmB | For parent compound, AmB: generally broad—most fungi | For parent compound, AmB:<br>*Aspergillus terreus*<br>*Trichosporon beigelii*<br>*Pseudallescheria boydii*<br>*Scedosporium apiospermum*<br>*Scedosporium prolificans*<br>*Malassezia furfur*<br>*Candida lusitaniae*<br>*Candida guilliermondii*<br>*Fusarium* spp<br><br>Potential for any species to be resistant | |
| Amphotericin B colloidal dispersion | 3–4 mg/kg IV qd; infuse at 1 mg/kg/hr | Invasive aspergillosis in patients refractory to or intolerant of AmB | Same as above | | Significant infusion-related side effects |
| Liposomal amphotericin B | 3–5 mg/kg IV qd; infuse over 1–2 hours | Empirical therapy in febrile neutropenia; cryptococcal meningitis in HIV-infected persons; *Aspergillus*, *Candida*, or cryptococcal infections in patients refractory to or intolerant of AmB; visceral leishmaniasis | Same as above | | Only liposomal AmB preparation; higher doses effective and well tolerated; 50 times more expensive than AmB |
| Liposomal nystatin | N/A; IV preparation | N/A | Similar to AmB | Similar to AmB | In phase III trials |
| **Triazoles** | | | | | |
| Voriconazole | IV: 6 mg/kg q12 hours x 2, then 4 mg/kg q 12 hours<br><br>Oral: 200 mg q 12 h for those ≥ 40 kg; 100 mg q 12 h for those < 40 kg | Invasive aspergillosis; serious infections due to *Scedosporium apiospermum* (the asexual form of *Pseudallescheria boydii)* and *Fusarium* spp in patients refractory to or intolerant of other therapy | Broad—extends coverage seen with AmB to *Scedosporium* and *Fusarium;* improved response for aspergillosis compared with AmB; enhanced activity against fluconazole-resistant *Candida* spp (including *C. krusei, C. glabrata, C. guilliermondii*) | Zygomycetes | Metabolized by cytochrome P450 system—many potential drug interactions; frequent visual disturbances, also rash and elevated levels of trans-aminases |
| Posaconazole | N/A<br>oral liquid–divided dosing improves absorption | N/A | Similar to voriconazole, but extends coverage to Zygomycetes | | In phase III trials |
| Ravuconazole | N/A<br>(oral formulation) | N/A | | Limited activity against Zygomycetes, *Fusarium*, *Pseudallescheria* | In phase II trials<br>High bioavail-ability and long half-life |
| **Echinocandins** | | | | | |
| Caspofungin | 70 mg loading dose* IV on day 1, then 50 mg IV qd<br><br>*no loading dose given for *Candida* esophagitis | *Candida* infections: esophagitis; Invasive: bloodstream infection, intra-abdominal abscess, peritonitis, pleural space infection; aspergillosis in patients refractory to or intolerant of other therapies | All *Candida* species: azole-resistant *Candida* spp, *Candida lusitaniae* | *Cryptococcus*<br>*Fusarium*<br>*Pseudallescheria boydii*<br>Zygomycetes | |
| Micafungin | *Candida* esophagitis: 150 mg IV qd; prophylaxis of *Candida* infections in SCT pts: 50 mg IV qd | *Candida* esophagitis; prophylaxis of *Candida* infections in SCT patients | Similar to caspofungin | Same as above | High therapeutic index, longer half-life |
| Anidulafungin | N/A<br>(IV formulation) | N/A | Data limited | Data limited | In phase II/III trials; extensive tissue distribution, longest half-life of the three |

Abbreviation: AmB = amphotericin B; SCT = stem-cell transplant

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