Echinocandins in the management of invasive fungal infections, part 2

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Place in therapy

Oropharyngeal and esophageal candidiasis. Oropharyngeal candidiasis can infect both immunocompetent and immunocompromised patients. Infants, patients with dentures or other oral devices, and patients receiving treatment with antibiotics, inhaled corticosteroids, or chemotherapy are frequently infected. Patients with xerostomia due to prior radiation, surgery, or autoimmune conditions are also at risk. Transplant recipients, patients with HIV/AIDS, and those receiving treatment with immunomodulating medication for any reason may also develop oropharyngeal candidiasis. In the absence of prior antifungal therapy, these patients generally can be easily treated with topical antifungal agents, since the majority of mucosal Candida infections are caused by fluconazole-susceptible C. albicans. The emergence of triazole resistance has been observed in patients with a history of triazole treatment and severe immunosuppression. In addition, non-C. albicans species may be isolated from the oropharynx of triazole-treated patients with severe immune defects. Esophageal candidiasis is most commonly diagnosed in patients...
with HIV, who may have dysphagia and odynophagia and often have coexistent oral thrush. Diagnosis can be made by esophageal gastroendoscopy (EGD), which reveals whitish plaques involving the mucosa that are identified as *Candida* species. This more invasive infection requires systemic antifungal therapy and is often initially treated with parenteral agents because of the patient’s severe dysphagia. Infection can be severe and recurrent, resulting in dehydration and cachexia due to poor oral intake. Empirical therapy with fluconazole is often initiated in patients with oropharyngeal candidiasis and esophageal symptoms, though EGD is indicated for those who do not have a clinical response.67,68

The treatment of invasive fungal infections is complicated by both host factors and the emergence of resistance to antifungal agents. Patients with recurrent esophageal candidiasis caused by fluconazole-resistant isolates can often be successfully treated with fluconazole.69 The presence of triazole-resistant mutations is therefore often difficult to predict. In addition, even selected antifungal susceptibility testing for mucosal isolates is costly and not widely available.

Guidelines for the management of candidiasis published by the Infectious Diseases Society of America in 2004 recommend the use of oral fluconazole capsules or itraconazole solution for the treatment of esophageal candidiasis.70 Caspofungin therapy is included in the alternatives for treatment of fluconazole-refractory disease, along with itraconazole solution and voriconazole. Intravenous amphotericin B deoxycholate is also offered as a therapeutic option. Treatment of esophageal candidiasis with any of the available echinocandins is unlikely to become the standard of care, given the lack of clinical superiority to justify the significant costs associated with these agents, as well as the absence of an oral formulation. In the event that echinocandin therapy is preferred, all three existing formulations will likely be clinically equivalent.71

The incidence of esophageal candidiasis itself has also declined dramatically in recent years with the introduction of highly active antiretroviral therapy (HAART), resulting in a decreased demand for antifungycotics that can be used for prophylaxis or treatment.72

Candidemia. Candidemia is the fourth most common cause of hospital-related bloodstream infections in the United States.73 The attributable mortality rate of 33–47% associated with invasive *Candida* infections is significantly higher than the mortality rate for the other major causes of nosocomial bloodstream infection.74–77 The echinocandins show considerable efficacy in vitro and in vivo in the treatment of candidemia and invasive candidiasis.78 Caspofungin received FDA-approved labeling for this indication in 2003. In vitro studies of caspofungin have demonstrated excellent activity against the majority of clinical isolates of *Candida* species, including organisms that are highly resistant to fluconazole.79 The activity of caspofungin against most *Candida* species is particularly important given the changing epidemiology of *Candida* species in patients diagnosed with candidemia. As the population of immunocompromised patients has expanded, fluconazole has been more widely used as prophylactic and empirical antifungal therapy. This practice appears to have contributed to a shift in the distribution of clinical isolates to a predominance of non-*C. albicans* species.80 Fluconazole-resistant *C. glabrata* and *C. krusei* infections can be treated with caspofungin. Patients at risk for triazole resistance because of prior triazole treatment, prolonged hospitalization, or severe immunosuppression are increasingly being treated empirically with echinocandins while awaiting culture data and fungal susceptibility test results.

A study comparing caspofungin to amphotericin B deoxycholate in 239 patients with positive *Candida* cultures from blood or another sterile site showed a successful clinical outcome in 73.4% of caspofungin-treated patients (80 of 109) versus 61.7% of amphotericin B recipients (71 of 115).82 There were fewer drug-related toxicities found in the caspofungin group than the amphotericin B group. Concern has been raised about the high rate of *C. parapsilosis* in 5 of the 9 patients in the caspofungin group who had persistently positive cultures, as opposed to 0 of the 10 patients with persistently positive cultures in the amphotericin B group. This may reflect the higher relative MICs of *C. parapsilosis*70 and *C. krusei*, along with the less commonly isolated *C. guilliermondii* and *Candida lusitaniae*,70,81 to caspofungin, though the relationship of MICs to clinical outcomes is complex and remains unclear.16

Invasive candidiasis. Candidemia can result in endocarditis, pericarditis, peritonitis, meningitis, osteomyelitis, and endophthalmitis. A recent increase in the rate of invasive candidiasis has been seen as a result of the expanding population of critically ill and immunocompromised patients, as well as the development of more invasive medical technologies.82 The most recent guidelines for the management of invasive candidiasis were extrapolated from clinical case series and anecdotal reports,70 and no randomized controlled trials in this patient population have been published to date. The manufacturer of caspofungin recently completed the enrollment of patients in a study of nonbloodstream *Candida* infections involving deep tissues and organs.83 Results from this multicenter trial should contribute to the limited information available regarding the use of antifungal agents in the treatment of invasive fungal disease.
The challenge of designing optimal antifungal regimens for patients with invasive candidiasis has not been simplified with the availability of standardized antifungal testing due to the failure of in vitro testing to correlate with clinical outcomes. There is clearly much more to be learned about the complex interaction between pathogenic fungal organisms and host defenses before the role of antifungal chemotherapy can be fully understood.

**Invasive aspergillosis.** *Aspergillus* species are ubiquitous opportunistic molds that cause life-threatening disseminated infections in immunocompromised patients. The overall fatality rate for invasive aspergillosis calculated from recent published case series is 58%, with rates of 86.7% for bone marrow transplant recipients and 88.1% for patients with disseminated or central nervous system disease. A recent review of 595 patients with proven or probable invasive aspergillosis identified a high rate of failure for all antifungal drugs (36%), with only 27% of treated patients demonstrating a complete response to treatment. The most recent practice guidelines addressing treatment choices antedated the release of the echinocandins and support aggressive use of the existing therapies at the highest recommended doses.

As difficult as invasive fungal infections are to treat, they can be even more challenging to diagnose. Patients at risk for such infections are often critically ill, with coexisting respiratory failure and thrombocytopenia that may limit the ability to obtain tissue cultures and pathology biopsy specimens. *Aspergillus* species are common environmental saprophytic molds that can contaminate microbiological culture specimens and colonize human tissues in the absence of infection. *Aspergillus* species are also the most common etiologic agents of invasive mold infections in the non-HIV-immunosuppressed patient population. Though organisms generally grow quickly and easily in the laboratory, *Aspergillus* cultures have a poor clinical sensitivity due to sampling error. Serologic studies, pathological evaluation of involved tissues, and radiographic imaging must be used to support the diagnosis of *Aspergillus* infection, since reliance on culture data may result in underdiagnosis, leading to catastrophic results. To standardize research studies and clinical reports of therapeutic options, a consensus statement was published by the European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group outlining standard definitions of invasive fungal infections to be used in clinical research. Criteria include host factors such as neutropenia, graft-versus-host disease, and prolonged corticosteroid therapy, as well as the presence of fever. Both microbiological and cytologic findings suggestive of invasive fungal infection are included, as well as specific serologic studies indicating the presence of fungal antigens. Specific findings on physical examination are used in conjunction with the results of diagnostic imaging studies to quantify the likelihood that an invasive fungal infection is present. These criteria have been used in studies and case reports of echinocandin use in the treatment of invasive mold disease and must be considered when evaluating therapeutic outcomes of antifungal therapy. These criteria of proven, probable, or possible invasive fungal infection can also help pharmacists to evaluate the appropriate use of echinocandin therapy in the absence of culture data or other definitive diagnostic information.

**Non-Aspergillus mold infections.** Infections caused by Cryptococcus, Trichosporon, and Zygomycetes are resistant to echinocandin therapy. Anidulafungin has not yet been studied in the treatment of unusual and refractory human invasive mold infections. Treatment failures have been reported when echinocandins were used as empirical therapy for patients whose fungal pathogen was later found to be resistant. Therapeutic failures are also seen when echinocandin therapy is used to treat susceptible fungal infections involving protected sites in which therapeutic levels may be difficult to achieve. Echinocandin therapy for endocarditis, endophthalmitis, meningitis, and osteomyelitis is not currently recommended because of the difficulty of reaching therapeutic levels at the site of infection using currently approved drug doses.

**Catheter-related infections.** Catheter-related infections are a major cause of nosocomial bloodstream infections in the hospitalized patient, especially in the ICU. Many of the pathogens responsible for these line-related or device-related infections exist in an extensive polysaccharide matrix called a biofilm. *Candida* species are the most common fungal pathogen associated with such infections. Biofilms formed by these pathogens are often quite resistant to many appropriately dosed antifungals and may partially contribute to the persistent candidemia experienced by some patients with infected devices. Caspofungin and micafungin have demonstrated activity against in vitro biofilm models infected with *C. albicans* and *C. parapsilosis*. In addition to the echinocandins’ favorable drug–drug interaction profile and nonrenal elimination, this activity suggests that the agents are attractive antifungals for the intensive care setting. However, caution must be taken because of the reduced activity of echinocandins against *C. parapsilosis*, which may justify extra clinical concern when managing intravascular infections caused by this organism. Catheter removal may be the most important therapy in the management of *C. parapsilosis* infections, as these are generally line-associated infections with a low attributable...
mortality. *C. parapsilosis* infections are rarely resistant to triazole treatment. **Prophylaxis in febrile neutropenia and HSCT.** The clinical spectrum and low toxicity of the echinocandins make them ideal candidates for use in a clinical regimen for the management of febrile neutropenia. The echinocandins are active against many triazole-resistant *Candida* species known to cause breakthrough infections in triazole-experienced patients with fever and neutropenia. The empirical use of caspofungin was evaluated in a study of 1095 patients with fever and neutropenia, with overall clinical success rates of 33.9% for 556 patients treated with caspofungin and 33.7% for 539 patients treated with liposomal amphotericin B (95.2% CI, –5.6 to 6.0%). The primary endpoints of breakthrough fungal infections and fever resolution were similar in both groups, though caspofungin’s success rate at 70 mg on day 1 and 50 mg thereafter (51.9%) was superior to that of liposomal amphotericin B 3 mg/kg daily (25.9%) (95% CI, 0.9–51.0, p = 0.04) in treating patients with baseline fungal infections (diagnosed within two days of study enrollment). This study established the noninferiority of caspofungin to a lipid formulation of amphotericin B for the empirical therapy of febrile neutropenia. The relatively low success rate of liposomal amphotericin B in this study, compared with previous success rates in studies of neutropenic fever, has raised important questions about antifungal dosing and the sequencing of antifungal prophylactic agents to optimize the management of this vulnerable patient population. Animal data suggest that triazole therapy followed by amphotericin B may be less optimal because of the similar targets of these two classes on the fungal cell membrane; this is not a concern with echinocandins.

Appropriate dosing is also a concern when antifungals are used as prophylactic therapy. The expense and toxicity of medications used to treat life-threatening infections can be easily justified, but it is far more difficult to determine the optimal dosage when the majority of patients receiving treatment do not have a documented infection. Drug and dose selection must be based on a full understanding of the individual patient’s risk of invasive fungal infection to ensure that resources are used appropriately and unnecessary toxicity is avoided.

The choice of empirical antifungal therapy as prophylaxis during the preengraftment neutropenic phase of HSCT is based on the same principles used to manage other neutropenic patients at risk. A study of micafungin sodium 50 mg i.v. daily (1 mg/kg for patients weighing less than 50 kg) in 882 patients undergoing HSCT established the superior efficacy of this agent over fluconazole 400 mg i.v. daily (8 mg/kg in patients weighing less than 50 kg) in a multicenter trial including both pediatric and adult patients. An overall efficacy of 80.0% in the micafungin population versus 73.5% in the fluconazole group was reported (95% CI, 0.9–12%, p = 0.03), with success defined as the absence of invasive fungal infection during prophylaxis and for four weeks after treatment. This study provided the scientific basis for FDA’s approval of micafungin’s labeling in March 2005 for antifungal prophylaxis for HSCT recipients. Recent guidelines for the treatment of invasive fungal infections in neutropenic patients have also been released supporting the use of micafungin.

Pharmacologic interventions often result in unexpected clinical outcomes when applied to a broad patient population. The success of voriconazole therapy in the treatment of invasive mold disease led to its early acceptance as a therapeutic option in the prophylaxis of HSCT patients. Reports have recently emerged from several centers that have had a significant increase in the frequency of Zygomycetes infections in this population. None of the echinocandins have activity against Zygomycetes, increasing the likelihood of such infections in immunocompromised patients treated with these agents for prophylaxis during prolonged neutropenia or after HSCT. Continued vigilance for such invasive mold infections is warranted at centers that incorporate echinocandin therapy into their prophylactic regimen.

The spectrum of echinocandin agents may provide unexpected prophylactic benefits in the HSCT population. The efficacy of these drugs in the eradication of the cyst form of *P. jirovecii* was established in the early development phase of the echinocandin class. This is not surprising given the structure of the *Pneumocystis* cell wall, which contains 1,3-β-glucan as a major constituent. Though the trophozoite form of *P. jirovecii* lacks this component, eradication of the cyst stage may provide effective prophylaxis against *P. jirovecii* pneumonia while avoiding the bone marrow suppression commonly seen with traditional trimethoprim–sulfamethoxazole prophylactic regimens. This potential advantage of echinocandin prophylaxis may be a target for future clinical studies, though the lack of an oral formulation will limit the usefulness of this indication after hospital discharge.

Now that the efficacy of a selection of antifungal agents has been established in preventing invasive fungal infections in patients with neutropenia and in HSCT patients, hospital pharmacies and individual prescribers must face the ethical dilemmas inherent in balancing the issue of cost with clinical benefit and toxicity. Algorithms may need to be developed to assist medical centers in objectively allocating these expensive yet effective therapies to those patients most likely to benefit from their use.
Use in solid organ transplant recipients. As echinocandins are prescribed more frequently for the prophylaxis and treatment of invasive fungal infections in solid organ transplant recipients, clinical experience with regard to toxicity issues is starting to be reported. Concerns about the hepatotoxicity of caspofungin may have limited its early use in this population. A review of 19 recipients of a solid organ transplant receiving concomitant caspofungin and immunomodulating therapy identified 2 patients with hepatotoxicity, both of whom were receiving other medications known to elevate liver enzymes. No dose-limiting hepatotoxicity was noted. The lack of drug interactions seen with the echinocandins is a major strength in the management of solid organ transplant patients, who often receive multiple immunosuppressant agents metabolized via the hepatic CYP system. However, there are reports of significant drug–drug interactions observed with caspofungin and tacrolimus. Please refer to the drug interaction section of this article for a more detailed discussion of the interaction between immunosuppressants and the echinocandins.

Prophylaxis in ICU patients. The echinocandin class of drugs has been studied in the treatment of highly immunocompromised patients; however, the bulk of drug use will likely be for the treatment of suspected or documented candidemia. Data have been accumulated that allow clinicians to predict which patients are at highest risk for candidemia, allowing targeted prophylactic treatment to be initiated in an attempt to prevent the morbidity and mortality associated with invasive candidiasis. Several randomized studies have been performed to evaluate the effect of fluconazole prophylaxis on the rate of fungal infections. A meta-analysis of these studies supports the success of fluconazole in preventing infection, but fails to demonstrate any survival advantage for the patients treated. Although the data analysis in this study was complex, particularly given the difficulties of determining the attributable mortality of fungal infections in a critically ill ICU population, it raises the question of the appropriateness of such prophylaxis. This issue is of particular concern with the increasing frequency of triazole-resistant Candida species in many ICUs. Though the echinocandins provide a safe and effective therapeutic option for prophylaxis in such patients, the cost of these agents may not be justifiable in the absence of clinical data to support their use. The Bacteriology and Mycology Study Group of the National Institute for Allergy and Infectious Diseases attempted to design a multicenter, blinded study of high-risk ICU patients to evaluate the efficacy of caspofungin versus placebo in decreasing the risk of invasive candidiasis. This study was recently closed because of difficulty with enrollment.

For now, hospital pharmacists and formulary committees must balance pressure from prescribing clinicians attempting to interpret the available data with the financial challenges common to many medical centers.

Combination therapy. As newer antifungal agents with unique mechanisms of action have been developed, scientific enthusiasm for combination therapy has resurfaced. The limited success of current regimens in eradicating invasive mold infection in the immunocompromised host makes this an obvious area for investigation, both in vitro and in vivo. Laboratory investigations of multiple combinations of antifungals in vitro are rapidly being translated into clinical practice for critically ill patients. Attempts to objectively approach therapeutic options scientifically are sometimes challenged by the urgency of patient management decisions and the relative lack of toxicity of newer agents. This is particularly true of the echinocandins, whose mechanism of action at the fungal cell wall has theoretic scientific potential for synergy with both polyenes and triazoles.

Invasive aspergillosis is a serious life-threatening infection associated with extremely high mortality rates in patients infected after cytotoxic chemotherapy or HSCT. With the development of newer antifungals, such as voriconazole and caspofungin, new salvage therapy regimens are being tested. A review of 47 patients with invasive aspergillosis who did not respond to initial therapy with amphotericin B formulations demonstrated an improvement in clinical outcome when treated with the combination of voriconazole and caspofungin compared with voriconazole monotherapy. Overall survival after diagnosis, as well as three-month survival after the initiation of the salvage regimen, was better in patients treated with combination therapy. Similar promise was seen in a retrospective evaluation of 30 patients treated with a combination of caspofungin and an amphotericin B formulation for a median duration of 24 days. All patients had fungal infections that did not respond to amphotericin B therapy. Of the patients treated with combination therapy, 60% had a favorable antifungal response, with 75% of leukemic patients (15 of 20) treated for fungal pneumonia responding favorably, with an antifungal response independent of the response to treatment of the patient’s underlying leukemia. Similar outcomes data were found during a retrospective analysis of 101 patients treated with the combination of caspofungin and liposomal amphotericin B, 48 of whom received at least 7 days of combination salvage therapy for documented or possible refractory invasive aspergillosis. The overall response rate was 42%, with an increased treatment failure rate among patients with documented rather than presumed Aspergillus infection, as well as among those
patients who did not receive at least 14 days of combination therapy. The caspofungin and liposomal amphotericin B combination resulted in a 38% response rate among patients with persistent neutropenia, a cohort that has often not responded to treatment in previous studies.\textsuperscript{120}

Animal data exploring the efficacy of combination therapy of invasive aspergillosis using an azole and an echinocandin were obtained early in the laboratory evaluation of micafungin. A trial of micafungin administered in combination with ravuconazole to a neutropenic rabbit model of invasive pulmonary aspergillosis demonstrated a significant improvement in mortality, residual fungal burden, and a measurable clinical marker of infection (serum galactomannan antigen) when compared with either drug alone.\textsuperscript{121}

Though animal data do not always correlate with human clinical drug efficacy, this convincing demonstration of antifungal synergy in vivo may have paved the way for early clinical trials of micafungin as part of a combination treatment regimen for the management of disseminated aspergillosis. Preliminary data were presented from an open-label study of micafungin added to existing antifungal therapy in the treatment of 85 bone marrow transplant recipients with proven and probable refractory aspergillosis.\textsuperscript{122} All patients received at least seven doses of micafungin, with a mean duration of micafungin therapy of 63 days. Treatment was initiated with micafungin sodium 75 mg i.v. daily, but dose escalation was permitted. The average daily dose in the study was 112 mg. Complete or partial response was seen in 39% of patients, with 89% of patients alive at the end of therapy and 33% alive at the end of the study. An independent review panel determined that 28% of the patients were successfully treated.\textsuperscript{122} A Phase II study evaluated the efficacy of micafungin as primary and salvage therapy in 283 patients with invasive aspergillosis, with outcomes data reported for both monotherapy (45% clinical response rate) and combination regimens (35% clinical response rate). Of the 120 patients in the salvage therapy group, 115 received combination therapy. This late employment of combination antifungal therapy in patients not responding to other regimens may not be the optimal test of clinical efficacy for this regimen.\textsuperscript{23} It is likely that the best patient outcomes will result from early and aggressive use of the most active antifungal agents. The successful outcomes reported when salvage treatments are added for patients who are not responding to their initial therapy may underestimate the potential effectiveness of an antifungal prescribed as primary therapy. Much of the mortality seen in invasive fungal infections occurs early, with less immunocompromised individuals surviving to derive benefit from the novel antimicrobials used.\textsuperscript{99}

A study of the safety and tolerability of combination therapy with anidulafungin and liposomal amphotericin B in 30 patients with invasive aspergillosis found that 17 of these patients had a total of 22 serious adverse events, only 2 of which were believed to be drug related.\textsuperscript{123} These included renal failure attributed to liposomal amphotericin B and abnormal liver function values. The study concluded that anidulafungin and liposomal amphotericin B can be safely used together in treatment.

The possibilities and limitations of combination antifungal therapy are just starting to be understood as experience with newer antifungals evolves. Preliminary research in this area indicates great potential for improved patient outcomes with the development of combination protocols, with few clinical reports suggesting antagonism. It is important, however, to make the distinction between the responsible prescribing of empirical therapy for life-threatening invasive fungal infections and the desperate employment of spiraling empiricism in an attempt to offer all therapeutic options to a terminally ill patient.\textsuperscript{124}

Hospital formulary restrictions and budgetary demands require that powerful new antimicrobials be allocated appropriately. More importantly, the ability of microorganisms to develop resistance to widely used antimicrobials has been well described in the fungal world, with the selective emergence of resistant non- \textit{C. albicans} species after the release of fluconazole. It is imperative that new antifungals be used responsibly so that their efficacy will be maintained.

\textbf{Discussion}

The expansion of the available antifungal armamentarium over the past decade has led to many debates among clinical mycologists regarding the optimal therapy for invasive fungal infections. Recent medical literature is replete with reviews of the newer agents\textsuperscript{125-127}; however, only time and experience will allow the prescriber to fully understand the strengths and weaknesses of these complex medications. Echinocandins may become the standard of care for the initial therapy of fungemia in medical centers or ICUs with a high rate of triazole-resistant \textit{Candida} infections. Cost considerations may drive the laboratory to provide early fungal species identification, allowing deescalation of therapy to oral fluconazole therapy when clinically indicated. It is unlikely that echinocandins will be adopted as initial monotherapy for proven invasive mold infections in immunocompromised patients, though their use in combination therapy continues to expand. The therapy of febrile neutropenia is evolving as the increasing use of antimicrobial and triazole prophylaxis before the onset of fever alters the microbial flora of the patient, potentially changing the epidemiology of their infections.
The use of preemptive antifungal therapy based on serial computed-tomography scanning and serum galactomannan testing may affect echinocandin use. The population of immunocompromised patients at risk for fungal infection is growing rapidly, providing economic incentives to the pharmaceutical industry to offer new therapeutic options.

Despite the great challenge of sifting through the medical literature in an attempt to optimize a clinical regimen for such complicated and critically ill patients, it is indeed a triumph of medical science that multiple antifungals with activity against fungal pathogens are available. The availability of effective, relatively nontoxic antifulgals is causing a paradigm shift in mycology practice, from the treatment-based days of amphotericin B deoxycholate to research into the prophylaxis and prevention of invasive fungal disease. As new pathogens are being identified in an expanding population of immunocompromised patients, the limited spectrum of the echinocandins may prove to be a detriment. Economic issues must also be considered with the addition of these agents to the formulary, particularly if they are used for antifungal prophylaxis or as a constituent of combination therapy. Despite these concerns, the echinocandins with their once-daily administration, limited toxicity, and minimal drug–drug interactions will clearly be part of the prophylactic and therapeutic management of invasive fungal infections for many years to come.

Conclusion

Echinocandins are fungicidal against yeast and fungastic against mold. Their limited toxicity profile and minimal drug–drug interactions make them an attractive new option for the treatment of invasive fungal infections. Their cost may limit their use as initial therapy for patients with fungemia in medical centers or ICUs with a high rate of triazole-resistant *Candida* infections.

References


