

Comparison of echinocandin antifungals

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Abstract: The incidence of invasive fungal infections, especially those due to *Aspergillus* spp. and *Candida* spp., continues to increase. Despite advances in medical practice, the associated mortality from these infections continues to be substantial. The echinocandin antifungals provide clinicians with another treatment option for serious fungal infections. These agents possess a completely novel mechanism of action, are relatively well-tolerated, and have a low potential for serious drug–drug interactions. At the present time, the echinocandins are an option for the treatment of infections due *Candida* spp (such as esophageal candidiasis, invasive candidiasis, and candidemia). In addition, caspofungin is a viable option for the treatment of refractory aspergillosis. Although micafungin is not Food and Drug Administration-approved for this indication, recent data suggests that it may also be effective. Finally, caspofungin- or micafungin-containing combination therapy should be a consideration for the treatment of severe infections due to *Aspergillus* spp. Although the echinocandins share many common properties, data regarding their differences are emerging at a rapid pace. Anidulafungin exhibits a unique pharmacokinetic profile, and limited cases have shown a potential for activity in isolates with increased minimum inhibitory concentrations to caspofungin and micafungin. Caspofungin appears to have a slightly higher incidence of side effects and potential for drug–drug interactions. This, combined with some evidence of decreasing susceptibility among some strains of *Candida*, may lessen its future utility. However, one must take these findings in the context of substantially more data and use with caspofungin compared with the other agents. Micafungin appears to be very similar to caspofungin, with very few obvious differences between the two agents.

Keywords: echinocandins, caspofungin, anidulafungin, micafungin, pharmacokinetics, antifungals

Introduction

Despite advances in medical practice, the incidence of invasive fungal infections has increased over the past 2 decades, such that *Candida* species are now the 4th most prevalent causative agent of nosocomial bloodstream infections (Wisplinghoff et al 2004), and infections caused by *Aspergillus* spp. are also increasing rapidly. Chandrasekar et al (2001) reported a steady increase in the frequency of clinical isolates of *Aspergillus* spp. from 1994 to 1999. Presumably, these trends are due to an increasing population of patients at risk for fungal infections, including patients with AIDS, solid organ and hematopoietic stem cell transplant recipients, and other patients at risk for immunosuppression (Clark and Hajjen 2002).

Over the past 10 years, a shift has occurred in the species of *Candida* causing bloodstream infections. According to national intensive care unit (ICU) data (from the National Nosocomial Infections Surveillance [NNIS] system), the percentage of fungal bloodstream isolates (BSI) due to *C. albicans* significantly decreased from 1989–1999, while the percentage of fungal BSI due to *C. glabrata* significantly increased (Trick et al 2002). In a recent multicenter observational study, non-*albicans* species constituted ~50% of bloodstream isolates, while *C. glabrata* was implicated in 21% of adult bloodstream isolates (Clark and Hajjen 2002; Pappas et al 2003).

Despite the introduction of newer, more potent antifungal agents, mortality due to fungal infections remains high. The attributable mortality due to nosocomial

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Candida bloodstream infections at one institution was not significantly different, when compared in two studies conducted 15 years apart (38% in 1983–1986 versus 49% in 1997–2001) (Gudlaugsson et al 2003). Meanwhile, mortality associated with invasive *Aspergillus* approaches 100% in some patient populations, including bone marrow transplant recipients (Lin et al 2001; McNeil et al 2001).

Fortunately, there has been a recent surge in antifungal drug development. Triazole agents with broad spectrums of action have arrived (voriconazole) and several more are in development. Some of these agents have expanded the azole spectrum of action to include fungi of the class *Zygomycetes* (posaconazole). The liposomal polyenes have combined the efficacy of amphotericin B with a decreased incidence and severity of side effects. Possibly most importantly, compounds with a completely novel mechanism of action have arrived, the echinocandins (caspofungin, micafungin, and anidulafungin).

Pharmacology Chemistry

The echinocandins are semisynthetic lipopeptides produced via chemical modification of natural products of fungi: caspofungin from pneumocandin B₀ from *Glarea lozoyensis*, micafungin from the hexapeptide FR901370 from *Coleophoma empedra*, and anidulafungin from echinocandin B₀ from *A. nidulans*, respectively (Carver 2004; Murdoch and Plosker 2004; Cancidas PI 2005).

Chemical structures of the currently Food and Drug Administration (FDA)-approved echinocandins are provided in Figure 1 (Boucher et al 2004). Echinocandins are cyclic hexapeptides with N-linked acyl lipid side chains and molecular weights of approximately 1200 (Abruzzo et al 1997; Mikamo et al 2000). Early investigation revealed that the position and conformation of this N-linked acyl side chain is crucial to the antifungal activity of the echinocandins. Interestingly, these fatty side chains were also implicated as a cause of hemolysis in early echinocandin compounds; subsequent modifications led to compounds with potent antifungal activity without hemolytic effects (Klein and Li 1999).

Mechanism of action of echinocandins

The echinocandins are concentration-dependent, non-competitive inhibitors of 1,3- β - and 1,6- β -D-glucan synthase, an enzyme complex composed of two subunits, encoded by the genes *FKS1* and *FKS2*. Glucan synthase is

involved in the synthesis of 1,3- β -D-glucan, a polysaccharide composed of 3 helically-entwined polymers of glucose. Despite substantial work to elucidate the precise location where echinocandins bind to the glucan synthase enzyme complex, this question remains unresolved. Glucan is an essential carbohydrate component of all fungal cell walls, comprising 30%–60% of the fungal cell wall in *Candida* and *Saccharomyces*. Changes in the characteristics of the cell wall can lead to osmotic instability and eventual cell lysis. Importantly, human cells do not contain 1,3- β -D-glucan, thus avoiding direct human cell toxicity (Klein and Li 1999; Deresinski and Stevens 2003; Carver 2004; Stevens et al 2006).

The proportion of the fungal cell wall composed of glucan varies widely between different species of fungi. 1,3- β -D-glucan is more predominant in the cell walls of *Candida* and *Aspergillus* species (especially *C. albicans* and *A. fumigatus*) than in yeast forms of dimorphic fungi. Likewise, the cell walls of mycelial forms of *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis* contain significant amounts of 1,3- β -D-glucan, while zygomycetes lack this target component. However, these characteristics do not always predict echinocandin activity. For example, the cell wall of *Cryptococcus neoformans* contains 1,3- β -D-glucan but the echinocandins demonstrate little activity against this pathogen. This suggests that there are likely additional (or alternate) components of the mechanism of action of the echinocandins (Feldmesser et al 2000; Maligie and Selitrennikoff 2005).

In vitro, caspofungin is fungicidal against *C. albicans*, causing lysis of growing and metabolically active cells (Bartizal et al 1997). However, its activity against *Aspergillus* is more complex: although caspofungin does not reduce the number of colony-forming units (CFU) of *A. fumigatus*, it causes significant injury, and perhaps lysis, to the hyphal tips of actively growing cells. It is postulated that this may prevent the organism from spreading beyond the initial site of infection. As such, caspofungin is considered fungistatic against *Aspergillus*, (as are the azole antifungals, although some in vitro work suggests that voriconazole may be fungicidal as well) in contrast to amphotericin B, which is fungicidal (Krishnan et al 2005). The clinical significance of these in vitro differences is not clear (Bowman et al 2002). However, a recent in vitro study in which phagocytic cells were combined with micafungin provides a potential (and logical) explanation for the confusing lack of correlation between in vitro and in vivo activity of echinocandins. In vitro combination of

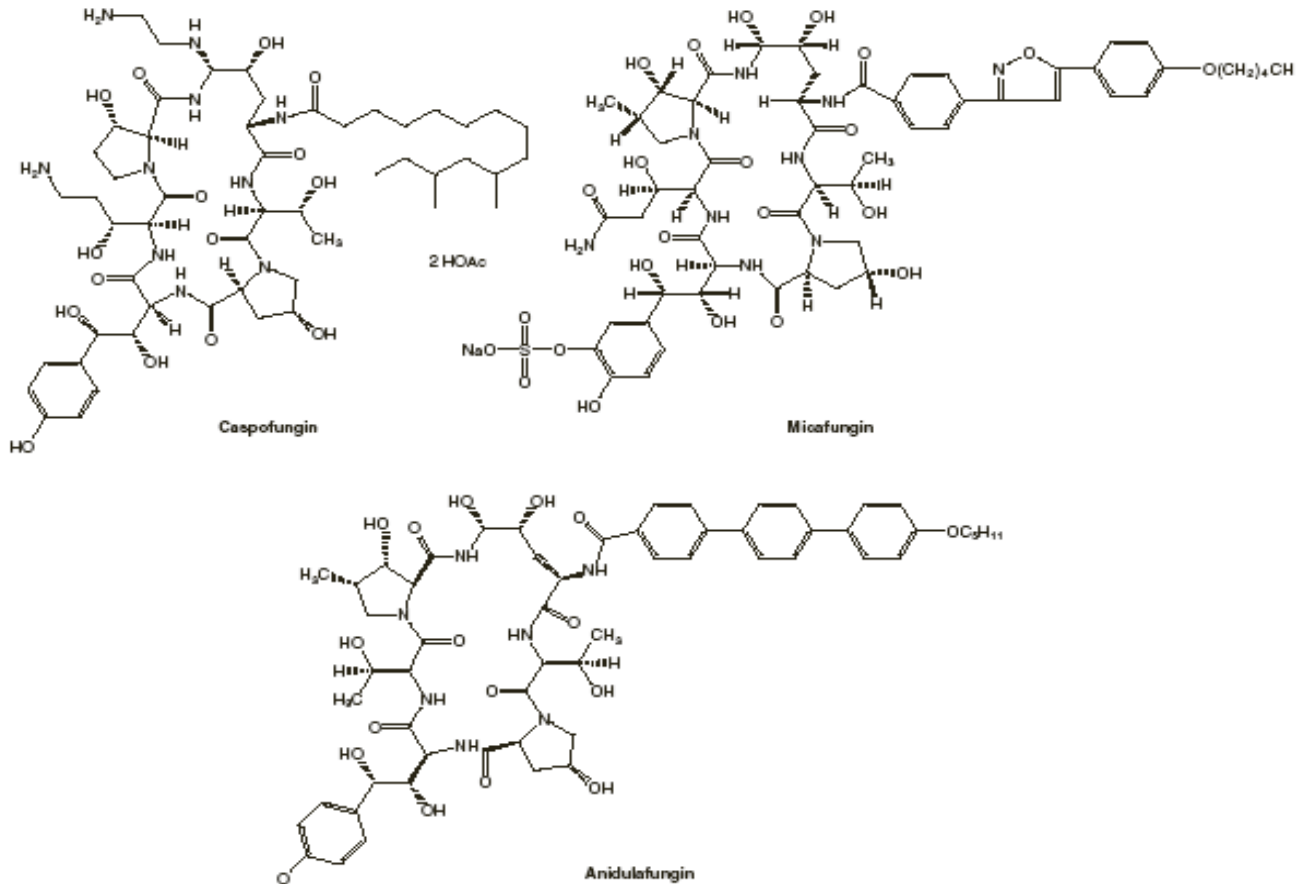


Figure 1 Structures of echinocandins. Copyright © 2004. Reproduced with permission from Boucher HW, Groll AH, Chiou CC, et al. 2004. Newer systemic antifungal agents: pharmacokinetics, safety and efficacy. *Drugs*, 64:1997-2020.

micafungin and phagocytes results in greater inhibition of *A. fumigatus* growth than either micafungin or various phagocytes by themselves (Choi et al 2004). Another study further demonstrated that pretreatment of polymorphonuclear leukocytes (PMNs) with granulocyte-macrophage colony-stimulating-factor (GM-CSF) increased the efficacy of the drug-immune component combination, resulting in synergy (Gil-Lamaignere et al 2004).

Biofilms often develop on prosthetic devices (eg, catheters), and *Candida* species, especially *C. albicans* and *C. parapsilosis*, are often implicated as causative agents. Biofilms develop in three phases: an early phase in which fungi attach to the surface of the device; an intermediate phase where blastospores aggregate to produce an extracellular matrix; and a maturation phase, during which fungi are incorporated into the matrix (Cocuaud et al 2005). In 96-well biofilm models, echinocandins, unlike azoles, appear to have potent activity against preformed *Candida*-

related biofilms. In addition, caspofungin prevents adherence of *C. albicans* to epithelial cells, inhibiting the early phase of development (Bachmann, VandeWalle, et al 2002; Soustre et al 2004). In silicone elastomer models of biofilm infection, caspofungin and micafungin are effective in killing *C. albicans* and *C. parapsilosis* biofilm cells (sometimes >99% of cells, even at concentrations achieved in vivo). Only amphotericin B lipid complex and liposomal amphotericin B express similar activity (Kuhn et al 2002). Interestingly, in the 96-well biofilm model, no evidence of synergy or additive effects were observed when fluconazole, amphotericin B, and caspofungin were used in combination against *C. albicans* biofilms (Bachmann et al 2003). These are important developments, since biofilm-related infection and colonization are very difficult to eradicate with azole antifungal therapy. Often, removal of the infected device is required (Ramage et al 2002). However, whether these in vitro models of biofilm infection are applicable to the clinical

setting is unknown, but merit further investigation for the therapy of biofilm-associated infections.

Spectrum of activity

Comparison of in vitro activity of echinocandins

Minimum inhibitory concentration (MIC) values should be interpreted cautiously as standardized methods to test the susceptibility of echinocandins have yet to be developed. Interpretive breakpoints, which help guide the clinician to make a correlation between in vitro susceptibility and in vivo outcomes, are not yet available and will require validation in clinical trials (Carver 2004). In vitro MIC studies with echinocandins have employed multiple methodologies, including differing inoculae, composition and pH of media, reading times (24 vs 48 hours), determination of MIC ("prominent" vs 80% or 90% inhibition of growth), and growth forms (yeast vs mycelium form). Kurtz and colleagues (1994) proposed the use of the minimum effective concentration (MEC) as a new endpoint of morphologic change for testing of caspofungin and other echinocandins. The MEC is defined as the lowest concentration of drug that causes the formation of microcolonies of the organism, or the lowest concentration at which a prominent decrease in turbidity occurs compared with the growth control (Kurtz et al 1994, Carver 2004)

As a class, the echinocandins demonstrate excellent activity against *Candida* spp. All 3 agents display higher MICs for *C. parapsilosis*, *C. lusitanae*, and *C. guilliermondii* compared with other *Candida* species (Pfaller, Boyken, et al 2005; Pfaller et al 2006). However, at this time, little correlation can be made between MICs and clinical outcomes with the echinocandins. In fact, a recent study showed that patients with *Candida* isolates displaying higher MICs (>2 µg/mL) had superior clinical outcomes compared with those with isolates displaying MICs <1 µg/mL (Kartsonis, Killar, et al 2005). A study which attempted to determine whether the in vitro MIC discrepancies between different *Candida* species (with *C. albicans* displaying significantly lower MICs than *C. parapsilosis* and *C. guilliermondii*) translated to differences in an in vivo murine kidney infection model found conflicting results. The isolate of *C. parapsilosis* that displayed the highest MIC to caspofungin responded in vivo to the lowest dose (1 mg/kg/day). Conversely, the two isolates with the lowest MICs only responded in vivo to the

highest dose (5 mg/kg/day). Predictably, however, the overall reduction of fungal burden was 100-fold less in the models infected with non-*albicans* isolates (Barchiesi et al 2006). The echinocandins demonstrate excellent in vitro activity against *Aspergillus* spp. An interesting component of the spectrum of the echinocandins is their in vitro activity against *Pneumocystis carinii* (*P. jirovecii*) (Ito et al 2000; Anonymous 2003; Pacetti and Gelone 2003). Interestingly, the echinocandins were originally developed in part because of their efficacy against *Pneumocystis* (Anonymous 2003; Denning 2003; Carver 2004). The echinocandins do not possess activity against the zygomycetes, *Fusarium solani*, *Scedosporium prolificans*, *Cryptococcus* spp, or *Trichosporon* spp. (Zaas and Alexander 2005). Although caspofungin, like other echinocandins, has minimal in vitro activity against the agents of mucormycosis when tested in vitro by standard techniques, the accuracy of current in vitro testing against molds remains unclear. *R. oryzae* expresses the target enzyme for echinocandins, and in the murine model of disseminated mucormycosis, caspofungin displayed limited activity against *R. oryzae* and the combination of caspofungin (1 mg/kg/day) plus amphotericin B lipid complex (5 mg/kg/day) was synergistic and resulted in significantly improved survival versus either therapy used alone. Nevertheless, clinical experience with echinocandins for these infections are limited (Spellberg et al 2005). While the echinocandins display activity against the mycelial forms of endemic fungi such as *Histoplasma* spp., *Blastomyces* spp., and *Coccidioides* spp., they display significantly higher MIC values against the yeast forms of these organisms (Wiederhold, Graybill, et al 2005). Finally, caspofungin was found to inhibit the growth (via 1,3-β-D-glucan synthase inhibition) of several rare molds, including *Alternaria* sp., *Curvularia* sp., *Scedosporium apiospermum* and *prolificans*, *Acremonium* sp., *Bipolaris* sp., and *Trichoderma* sp. (Kahn et al 2006).

Susceptibility breakpoints have not been determined for the echinocandins. In general, the echinocandins display MIC₉₀ values (MIC required to inhibit growth of 90% of organisms) of ≤2 µg/mL against *Candida* spp. A review by Zaas and Alexander (2005) succinctly compares the MIC values of the echinocandins, and illustrates that in general, anidulafungin displays the lowest MIC values against most *Candida* spp., followed by micafungin and then caspofungin.

Anidulafungin displays low MICs against strains of *C. parapsilosis* with high MICs to caspofungin and micafungin and limited cases have shown a potential for activity in

isolates with increased MICs to caspofungin and micafungin (Ghannoum et al 2005). In addition, recent data reveals that isolates of *C. glabrata* with elevated MICs to caspofungin (8 µg/mL to 64 µg/mL) still display low MICs to anidulafungin (2 µg/mL to 4 µg/mL) (Wiederhold, Graybill, et al 2005). These results are interesting, and suggest that anidulafungin may be more potent against certain resistant *Candida* isolates when compared with the other echinocandins. However, these results must be corroborated with clinical data due to the lack of correlation of MICs with treatment outcomes. In addition, the presence of human serum decreases the in vitro potency of all the echinocandins and neutralizes the in vitro MIC superiority of micafungin over caspofungin (Park et al 2006).

Resistance to echinocandins

Although spontaneous resistance of *C. albicans* to echinocandins has been documented in vitro, the specific mechanisms of resistance have not been fully elucidated and prospective worldwide surveillance of clinical *Candida* isolates has revealed no evidence of emerging caspofungin resistance (Kurtz et al 1996; Pfaller et al 2006). The molecular target of echinocandins is the *FKSI* subunit of glucan synthase; predictably, mutations to this site confer varying degrees of resistance to the echinocandins (Douglas et al 1997). Recently, in vitro analysis of spontaneous mutants of *C. albicans* has implicated this mechanism as an important determinant of resistance (Balashov et al 2006). In addition, analysis of a *C. albicans* strain (MIC=8 mg/L) in a patient with recurrent esophagitis revealed a single amino acid substitution (serine-to-proline) at position 645 of the *FKSI* gene (Miller et al 2006). However, Hakki and colleagues (2006) recently published a case of *C. krusei* endophthalmitis and oropharyngeal candidiasis in which the isolate displayed reduced susceptibility to all three echinocandins, and was not mediated by a mutation of *FKSI*. In addition, recent analysis of *C. albicans* isolates with reduced echinocandin susceptibility found that overexpression of the RER1 (Regulator of Echinocandin Resistance) gene conferred resistance through an unclear pathway (Ketko et al 2006).

Converse to the echinocandins, azole antifungals block synthesis of lanosterol demethylase, which is encoded by *ERG11*. Alteration in this gene may confer decreased susceptibility to azoles. Upregulation of multidrug efflux pumps coded for by multidrug resistance (*MDR*) or *Candida* drug resistance (*CDR*) genes may also confer decreased azole activity. Theoretically, caspofungin activity should not

be affected by these mechanisms of azole resistance. Indeed, Bachmann, Patterson, and colleagues (2002) demonstrated that caspofungin was highly active against 32 isolates of both fluconazole susceptible- and resistant-*C. albicans*, including those possessing alterations of the *ERG11* and/or *CDR/MDR* genes. However, overexpression of *CDR2* efflux can result in increased MICs to echinocandins (Shuetzer-Muehlbauer et al 2003). In *C. glabrata*, upregulation of *CDR1* pumps does not confer reduced susceptibility to caspofungin (Katiyar et al 2005). Finally, Paderu and colleagues (2004) have shown that a high-affinity, saturable, facilitated-diffusion transporter mediates caspofungin entry into *C. albicans*. Disruption of this system represents a potential mechanism of resistance.

Resistance mechanisms have also been elucidated for several other fungal organisms. Overexpression of *Sbe2p*, a Golgi protein which is involved in cell wall construction, may confer resistance to caspofungin in *Saccharomyces cerevisiae* (Osherov et al 2002). In vitro resistance to *A. fumigatus* has been documented, with one strain demonstrating a target-site mutation which conferred low-level resistance. Another strain, deemed resistant, in fact demonstrated an “Eagle-like” effect (described below) (Gardiner et al 2005). Finally, as mentioned previously, echinocandins do not display in vitro or in vivo activity against *Cryptococcus neoformans*. Maligie and colleagues (2005) attempted to determine if the mechanism of this lack of effect was due to 1,3-β-D-glucan synthase resistance to echinocandins. Surprisingly, the authors found that the synthase enzyme was sensitive to caspofungin, although less so than for *C. albicans*. As such, the mechanism of *Cryptococcus neoformans* resistance to echinocandins is still unknown (Maligie and Selitrennikoff 2005).

Several case reports have documented echinocandin-resistant *Candida* spp. in the clinical setting. An AIDS patient with thrush and esophagitis (due to *C. albicans*) refractory to therapy with fluconazole and amphotericin B lipid complex initially responded to caspofungin monotherapy, but when therapy was discontinued, the infection returned. Subsequent therapy with caspofungin eventually failed. Serial isolates demonstrated caspofungin MICs of 0.25 mg/mL and >64 mg/mL in the first and final isolates, respectively. Although the utility of MIC values with caspofungin have been questioned, this case nevertheless presents an intriguing picture (Hernandez et al 2004). In a second case, a patient with prosthetic valve endocarditis due to *C. parapsilosis* was initially treated with amphotericin B (0.7 mg/kg/day) + flucytosine for 7 days;

therapy was then changed to caspofungin + intravenous fluconazole. The initial fungal isolate displayed low MICs to caspofungin and anidulafungin (2 µg/mL and 1 µg/mL, respectively), but a high MIC (8 mg/mL) to micafungin. After 6 weeks of therapy and sterile blood cultures, the patient was discharged on chronic, suppressive therapy with oral fluconazole. The patient was re-admitted 3 months later with *C. parapsilosis* which was resistant to fluconazole and voriconazole, had high MICs to caspofungin and micafungin (>16 mg/mL), yet retained activity to anidulafungin and amphotericin B. This case raises many questions about echinocandin resistance that remain unanswered. Especially intriguing is whether resistance to certain echinocandins confer cross-resistance to others or to the entire class, and whether azole resistance is mediated via mechanisms that may result in reduced susceptibility to echinocandins (Moudgal et al 2005). In addition, this case, combined with newer data, raises the question of whether anidulafungin has superior activity against *C. parapsilosis*. In a recent study, researchers examined several caspofungin-resistant isolates of *C. parapsilosis* from patients in a burn unit. The investigators found that certain isolates displayed MICs of 64 µg/mL to caspofungin and micafungin, yet displayed MICs of 1–2 µg/mL to anidulafungin. In addition, treatment with caspofungin did not affect the cellular structure, while treatment with anidulafungin caused cell lysis (Ghannoum et al 2005).

Finally, an interesting “Eagle-like” effect has been observed in vitro with caspofungin, whereby higher drug concentrations do not result in a greater degree of killing when compared with lower drug concentrations. When exposed to therapeutic concentrations of caspofungin, growth of *C. albicans* ceases. Paradoxically, exposure to supratherapeutic concentrations of caspofungin results in significant growth. This can occur either dramatically, in which the number of colonies is too numerous to count, or more subtly, where seemingly only a small number of cells are able to survive (the so-called “mini-paradoxical effect”). However, increasing the concentration even further results in cessation of growth, suggesting that the resistance can eventually be overcome. Investigators hypothesize that the phenomenon may be due to selection of derepressed resistance mechanisms, which require high concentrations of drug to “turn-on.” Interestingly, when isolates which illustrated this effect with caspofungin were tested against micafungin and anidulafungin, the “Eagle-like” effect was not observed (Stevens et al 2004, 2005). Subsequent studies support the hypothesis that when *C. albicans* is exposed to

high caspofungin concentrations, genes encoding chitin, a key cell wall polymer which is not targeted by caspofungin, are rapidly and transiently induced to compensate for the decreased synthesis of β -1,3- and β -1,6-glucan. Interestingly, it appears that the presence of a calcineurin inhibitor such as cyclosporine, inhibits this effect (Wiederhold, Kontoyiannis, et al 2005; Stevens et al 2006).

In in vivo models, the “Eagle-like” effect was observed in a rabbit model of invasive pulmonary aspergillosis, where caspofungin doses ≥ 3 mg/kg/day were associated with poorer survival (Petraitiene et al 2002). In a murine model of invasive pulmonary aspergillosis, a concentration-dependent reduction in mean pulmonary fungal burden was observed following single intraperitoneal doses of caspofungin of 0.25 mg/kg, 1.0 mg/kg, and 4.0 mg/kg. When mice were treated for 96 hours with the same dosages fractionated into 3 different dosing intervals (every 6, 24, or 48 hours), a concentration-dependent reduction in mean pulmonary fungal burden was observed in the 1 mg/kg dosage-fractionation group, with significantly lower mean pulmonary fungal burden in mice dosed every 48 hours versus every 6 hours. However, a paradoxical increase in pulmonary fungal burden was observed in the highest dosage-fractionation group (Wiederhold et al 2004). However, recent studies offer conflicting results. Addition of mouse serum to an in vitro model eliminated the paradoxical effect (Abruzzo et al 2005). In a study assessing whether the in vitro effect observed with several isolates could be duplicated in an in vivo mouse model, no paradoxical effect was observed following administration of doses ranging from 0.01 mg/kg to 20 mg/kg, no paradoxical effect was observed. However, a type of “cap effect” was seen in certain isolates, whereby increasing the dose higher than 0.5 mg/kg did not result in increased killing (Clemons et al 2006).

At this time, many questions remain regarding the mechanisms of resistance to the echinocandin antifungals. Fortunately, the echinocandins have proven to be worthy options in the treatment of azole-resistant *Candida* infections (further highlighted in clinical studies presented below), and clinical resistance remains a rare occurrence. However, clinical examples do raise interesting questions regarding cross-resistance among the echinocandins, and the potential role of anidulafungin in resistant isolates. Again, however, it is important to stress that differences based on echinocandin MICs should be interpreted with caution. Finally, it is unknown whether the interesting “Eagle-like” effect observed in some in vitro models translates into a

meaningful clinical effect as human studies have not been performed. However, supratherapeutic plasma concentrations utilized in in vitro studies have been observed in pharmacokinetic studies in healthy volunteers, and may be expected to occur in patients if larger doses of echinocandins are employed in future studies.

Pharmacokinetics of echinocandins

As a class, the echinocandins possess many pharmacokinetic similarities, including low oral bioavailability, high protein binding, and relatively low CSF and urine concentrations of parent drug (Table 1). Since urine concentrations of echinocandins (or active metabolites) are minimal, their clinical utility in treating urinary infections may be poor. One study reviewed the response of 12 patients with *Candida* urinary tract infections enrolled in 2 caspofungin trials. The number of patients who responded favorably (11/12) appears impressive. However, the limitations of the study (retrospective, small patient numbers), compounded by the difficulty in assessing true drug effect (since many fungal urinary tract infections resolve without therapy), limit the clinical utility of this data (Kartsonis et al 2003). All echinocandins display linear pharmacokinetics following

administration of intravenous dosages, and are degraded primarily by the liver (also in the adrenals and spleen) by hydrolysis and N-acetylation (Denning 2003). Following initial distribution, echinocandins are taken up by red blood cells (micafungin) and the liver (caspofungin and micafungin) where they undergo slow degradation to mainly inactive metabolites, although two uncommon metabolites of micafungin possess antifungal activity. Degradation products are excreted slowly over many days, primarily via the bile (Denning 2003). Fecal recovery data with radiolabeled micafungin in healthy subjects, demonstrate that approximately 40% of a 28mg dose is eliminated as parent drug and metabolites in the bile. In an interesting report of the successful treatment of a patient with candidal cholangitis with caspofungin, the biliary concentration of caspofungin was ~30% that of serum (Goicoechea et al 2004). This finding is not surprising considering the evidence that caspofungin utilizes the OATP-1B1 transporter, which also transports bile, rifampin, and cyclosporine (Sandhu et al 2005). Although it is not known whether micafungin or anidulafungin also utilizes this pathway, it appears unlikely since they interact less with cyclosporine than does caspofungin (van Burik et al 2004;

Table 1 Pharmacokinetic parameters of echinocandins in adult subjects (Denning 2003; Deresinski and Stevens 2003; Wiederhold and Lewis 2003; Carver 2004; Murdoch and Plosker 2004; Raasch 2004; Zaas and Alexander 2005)

Variable	Caspofungin	Micafungin	Anidulafungin
C_{max} (mg/L)(50 mg single dose)	7.64	4.95	2.07–3.5
Bioavailability			2%–7%
t_{1/2} (hours)	9–11	11–17	24–26
Vd (L/kg)	0.14 [9.67L]	0.215–0.242	0.5 [30–50L]
AUC (mg•h/L)	87.9–114.8	111.3	44.4–53
Protein binding (%)	96–97	99.8	84
Metabolism	Via slow peptide hydrolysis and N-acetylation. Also spontaneously degrades to inactive product	Via catechol-O-methyltransferase pathway	Not metabolised; undergoes slow chemical degradation to inactive metabolites
Cl_T (mL/min/kg)	0.15	0.185	0.26
f_e	1.4 %	0.7%	<1%
Elimination	35% feces, 41% urine (~1.4% as unchanged drug)	40% feces, <15% urine	Primarily in feces (<10% as intact drug), 1% urine
CSF penetration (% of plasma)	? low	? low	< 0.1 %
Dosage adjustment in renal insufficiency	No significant changes in PK. No dose adjustment needed.	No significant changes in PK. No dose adjustment needed.	No change in PK observed. No dose adjustment needed.
Dosage adjustment in hepatic insufficiency	Child-Pugh 5–6: none Child-Pugh 7–9: Significant increase in AUC. Reduce maintenance dose to 35 mg/day Child-Pugh >9: no data	Moderate dysfunction (Child-Pugh 7–9): C _{max} , Cl not significantly altered, AUC significantly decreased compared with healthy subjects.	No dose adjustment needed

Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; Cl_T, total clearance; C_{max}, maximum concentration; CSF, cerebrospinal fluid; f_e, fraction of drug excreted unchanged in the urine; PK, pharmacokinetic; t_{1/2}, elimination half life; Vd, volume of distribution.

Dowell et al 2005). None of the echinocandins serve as substrates, inducers, or inhibitors of cytochrome P450 enzymes, or the P-glycoprotein transport system (Denning 2003).

Echinocandins are available only as parenteral formulations, are not dialyzable, and do not require dosage adjustment in patients with renal insufficiency. They have minimal cerebrospinal fluid (CSF) penetration, largely due to their high protein binding and large molecular weights, although the clinical relevance of these findings may be disputed, given that several other antifungal agents (amphotericin B and itraconazole) are effective for the treatment of fungal meningitis despite low CSF concentrations (Denning 2003). However, one case report documents failure of caspofungin in the treatment of *Candida* endophthalmitis, presumably due to undetectable intravitreal concentrations of caspofungin. The patient was subsequently cured after therapy with 5 mg/kg/day amphotericin B lipid complex (Gauthier et al 2005).

Interesting disparities do exist between the agents, however. Among the echinocandins, anidulafungin is unique in being eliminated almost exclusively by slow chemical degradation rather than undergoing hepatic metabolism. Anidulafungin has a lower maximum concentration (C_{max}) and degree of protein binding, and much longer half-life and larger volume of distribution than the other two agents (Raasch 2004).

Pharmacokinetics of echinocandins in special populations

Renal insufficiency

As mentioned above, the echinocandins do not require dosage adjustment in patients with renal insufficiency.

Hepatic insufficiency

The echinocandins have been studied in patients with varying degrees of hepatic dysfunction. The area under the concentration-time curve (AUC) of caspofungin is significantly increased in patients with moderate (Child-Pugh 7–9) hepatic insufficiency (Stone et al 2001; Cancidas PI 2005). By contrast, the AUC of micafungin is decreased in patients with moderate insufficiency; this is likely to be due to an increased volume of distribution and lower protein binding in these populations (Hebert, Smith, et al 2005; Mycamine PI 2005). Anidulafungin concentrations were not increased in subjects with mild (Child-Pugh 5–6), moderate, or severe (Child-Pugh >9) hepatic insufficiency. Though a slight decrease in AUC was observed in patients with severe

hepatic insufficiency, it was within the range of population estimates noted for healthy subjects (Eraxis PI 2006).

Thus, it is suggested that the maintenance dose of caspofungin be decreased from 50 mg to 35 mg daily in patients with moderate hepatic insufficiency (Cancidas PI 2005). In patients receiving micafungin, dosage adjustments are not recommended for patients with moderate hepatic dysfunction (Mycamine PI 2005). Dosage adjustments are not suggested for patients with mild, moderate, or severe hepatic dysfunction who are receiving anidulafungin (Eraxis PI 2006). Presently, as there is limited experience with caspofungin and micafungin in patients with severe hepatic insufficiency, recommendations for dosage adjustments cannot be made at this time (Cancidas PI 2005; Mycamine PI 2005).

Pediatrics

Caspofungin

Limited information is available regarding the use of caspofungin in pediatric patients. The pharmacokinetics of caspofungin in 39 children (2–11 years old) and adolescents (12–17 years old) with neutropenia were compared with those of adults who had received 50 mg or 70 mg daily for mucosal candidiasis. After multiple doses, weight-based dosing (1 mg/kg/day) in children (only two adolescents were studied in the 1 mg/kg/day group) resulted in significantly lower plasma concentrations compared with those achieved in adults. However, in both children and adolescents, dosing based on body surface area (50 mg/m²/day) resulted in an area under the plasma concentration-time curve at steady state (AUC_{ss}) similar to those achieved in adults receiving 50 mg daily (Walsh et al 2005). In addition, a recent study evaluating caspofungin therapy in 6 neonates with invasive candidiasis revealed that doses of 2 mg/kg/day (or 25 mg/m²/day) resulted in similar plasma concentrations as those in adults receiving 50 mg daily (Odio et al 2005).

Micafungin

In a Phase I, sequential group dose-escalation study in pediatric patients, a 1.3- to 1.5-fold increase in the clearance of micafungin was noted in patients 2–8 years of age. As such, they recommended that a dosage of 1.5 times that of the adult dosage be utilized in this population (Seibel et al 2005).

Anidulafungin

The pharmacokinetics of anidulafungin after daily doses were investigated in immunocompromised pediatric (2–11 years) and adolescent (12–17 years) patients with

neutropenia. Steady state plasma concentrations were achieved on the first day after administration of the loading dose (twice the maintenance dose). C_{max} and AUC_{ss} increased in a dose proportional manner. Concentrations and exposures following administration of maintenance doses of 0.75 mg/kg/day and 1.5 mg/kg/day were similar to those observed in adults following maintenance doses of 50 mg/day and 100 mg/day, respectively (Eraxis PI 2006).

Nursing mothers

Caspofungin, micafungin, and anidulafungin can be found in the milk of lactating, drug-treated rats; it is not known whether they are excreted in human milk. Caution should be exercised when echinocandins are administered to a nursing woman (Mycamine PI 2005; Cancidas PI 2005; Eraxis PI 2006).

Pregnancy

The echinocandins are all categorized as Pregnancy Category C. Anidulafungin and caspofungin cross the placental barrier in rats and are detected in fetal plasma. There are no adequate and well-controlled studies in pregnant women; thus, echinocandins should be used only if the potential benefit justifies the risk to the fetus (Mycamine PI 2005; Cancidas PI 2005; Eraxis PI 2006).

Geriatric use

Dosage adjustments are not required for geriatric patients receiving echinocandins (Mycamine PI 2005; Cancidas PI 2005; Eraxis PI 2006). In clinical studies of micafungin, a total of 186 subjects were 65 years of age and older, and 41 subjects were 75 years of age and older. The exposure and disposition of a 50mg micafungin dose administered as a single 1 hour infusion to 10 healthy subjects aged 66–78 years were not significantly different from those in 10 healthy subjects aged 20–24 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Plasma concentrations of caspofungin in healthy older men and women (≥ 65 years of age) were increased slightly (approximately 28% in AUC) compared with young healthy men. A similar effect of age on pharmacokinetics was seen in patients with candidemia or other *Candida* infections (intra-abdominal abscesses, peritonitis, or pleural space infections). No dose adjustment is recommended for the elderly; however, greater sensitivity of some older individuals cannot be ruled out.

In population pharmacokinetic analyses of anidulafungin, the median clearance differed slightly

between the elderly group (patients ≥ 65 , median clearance (CL)=1.07 L/h) and the nonelderly group (patients < 65 , median CL=1.22 L/h); however, the range of clearance was similar.

Race and gender

The pharmacokinetics of echinocandins are similar among Caucasians, Blacks, Asians, and Hispanics. Dosage adjustments are not required based on race (Cancidas PI 2005; Mycamine PI 2005; Eraxis PI 2006).

Pharmacodynamics of echinocandins

The echinocandins exhibit concentration-dependent killing. In a murine model of systemic candidiasis, the pharmacodynamic parameter that predicted efficacy with caspofungin was the ratio of the area under the curve to the minimal inhibitory concentration (AUC/MIC) (Louie et al 2005). Caspofungin efficacy against *C. albicans* persists even after serum concentrations fell below the MIC, suggesting that caspofungin concentrations in tissues remain high even after serum concentrations have declined (or that caspofungin displays a significant post-antifungal effect) (Louie et al 2005). In fact, a study utilizing time-kill experiments found that when *Candida* is exposed to caspofungin for only one hour (followed by drug washout), virtually equivalent killing is achieved as when compared with caspofungin exposure for 24 hours. In addition, *Candida* growth is inhibited for at least 24 hours following drug washout (Clancy et al 2006). In another animal model with an experimental glucan synthase inhibitor, HMR 3270, antifungal efficacy was predicted by the ratio of the C_{max} to the MIC (C_{max} :MIC). A C_{max} :MIC of 3 resulted in fungistatic activity but fungicidal activity was not observed until the C_{max} :MIC ratio approached 10 (Andes et al 2003). In the murine model of invasive pulmonary aspergillosis described above (Wiederhold et al 2004), C_{max} :MEC was the parameter most closely associated with the reduction of pulmonary fungal burden. Finally, the activity of anidulafungin against *C. albicans* and *glabrata* in a neutropenic murine disseminated candidiasis model was found to be greatest when administered as large, infrequent doses (Andes and Marchillo 2006).

Drug interactions with echinocandins

The echinocandins are not appreciable substrates, inhibitors, or inducers of cytochrome P450, nor do they interact with P-glycoprotein, as do some of the triazole antifungals. Although micafungin is a substrate for and a weak inhibitor of CYP3A in vitro, hydroxylation by CYP3A is not a major

pathway for micafungin metabolism in vivo. (Mycamine PI 2005; Sakaeda et al 2005). As such, as a class, echinocandins are expected to demonstrate a low capability for producing drug–drug interactions. This has generally proven true. No effect on cyclosporine metabolism was noticed in vitro, and an in vivo study evaluating a potential interaction between cyclosporine and anidulafungin revealed only a clinically insignificant 22% increase in the AUC of anidulafungin following 4 days of concomitant cyclosporine therapy (Dowell et al 2005). Concurrent administration of rifampin or a variety of other (204 substrates, 140 inhibitors, and 40 inducers of CYP450) agents with anidulafungin does not affect the clearance of anidulafungin (Dowell et al 2004).

Several studies have evaluated the interaction of micafungin with various immunosuppressants. Although micafungin does not significantly affect the clearance (or AUC) of tacrolimus (Hebert, Blough, et al 2005), it increases the AUC of sirolimus by 21% and decreases the clearance of cyclosporine by 16% (Hebert, Townsend, et al 2005; Mycamine PI 2005). This alteration in cyclosporine clearance was deemed clinically insignificant by the investigators. However, since 5 of 28 (18%) subjects in the study experienced a clinically significant (>25%) change in clearance, the authors suggested monitoring cyclosporine levels during combination therapy with micafungin. The package insert also states that micafungin increases the AUC of nifedipine by 18%, entailing the need for close monitoring of an increased effect of nifedipine (Mycamine PI 2005).

Predictably, the most data exists with caspofungin. One group of authors hypothesized that since the metabolic transformation of caspofungin is slow, perhaps the process is limited by hepatocyte drug uptake transporters. Indeed, several in vitro experiments demonstrated that the hepatic transport protein OATP-1B1 may be responsible for hepatic uptake of caspofungin (Sandhu et al 2005). Since cyclosporine is a known substrate of this transporter, this offers a possible (albeit unproven) explanation for its interaction with caspofungin. Indeed, cyclosporine has been shown to increase the AUC of caspofungin by ~35% (Cancidas PI 2005). Similarly, rifampin (an inhibitor of OATP-1), has been shown to both inhibit and induce caspofungin metabolism. During the first day of rifampin co-administration, a transient 61% increase in the AUC of caspofungin is observed; however, when assessed after 14 days of rifampin administration, a 14%–31% reduction in caspofungin troughs is observed. Therefore, the authors recommend an increased dose of caspofungin during

concomitant administration with rifampin (Stone et al 2004). A dosage increase is recommended in patients receiving other enzyme inducers, such as efavirenz, nevirapine, phenytoin, dexamethasone, and carbamazepine. Finally, tacrolimus AUC, peak, and 12-hour concentrations are decreased by approximately 20% during concomitant administration with caspofungin, potentially necessitating more frequent monitoring. The mechanism for this interaction has not been elucidated (Cancidas PI 2005).

When reconstituting anidulafungin, 20% dehydrated alcohol must be utilized (60 mL or 30 mL for 200 mg or 100 mg doses, respectively). This may be a concern for several patient populations, such as those susceptible to disulfiram reactions (for example, patients receiving concurrent metronidazole use), or for patients who are recovering alcoholics (Eraxis PI 2006).

Safety and adverse effects of echinocandins

All three echinocandins are generally well-tolerated. The most common adverse effects are listed in Table 2. While there appear to be some differences between the agents, it is important to keep in mind that caspofungin has been on the market much longer than both micafungin and anidulafungin. As such, it is difficult to derive conclusions or make valid comparisons between available echinocandins based on such small numbers of adverse effects. Finally, limited experience suggests that caspofungin and micafungin are safe to use in pediatric patients (Odio et al 2004; van Burik et al 2004; Groll et al 2005; Walsh et al 2005). The safety and effectiveness of anidulafungin in pediatric patients has not been established (Eraxis PI 2006).

At the time of FDA approval, there were concerns regarding the safety of caspofungin when combined with cyclosporine. In initial studies utilizing a combination of cyclosporine and caspofungin in 12 healthy volunteers, 5 experienced elevations in serum aminotransferase levels ≤ 3 times the upper limit of normal (ULN). In addition, 3 of 4 healthy subjects who received caspofungin 70 mg daily for 10 days plus two 3 mg/kg doses of cyclosporine on day 10 experienced transient increases in alanine transferase (ALT) on day 11 that were < 5 times the ULN. In the same study, 2 of 8 subjects who received caspofungin 35 mg daily for 3 days and two 3 mg/kg doses of cyclosporine on day 1 experienced increases in ALT < 2 times ULN on day 2. As such, the package insert recommended that liver function tests be monitored closely when this combination is used (Cancidas PI 2005). However, recent data suggests that this

Table 2 Adverse effects of echinocandins (Sable et al 2002; Carver 2004; Raasch 2004; Krause, Reinhardt, et al 2004; Cancidas PI 2005; Groll et al 2005; Mycamine PI 2005; Eraxis PI 2006)

Parameter	Caspofungin	Micafungin	Anidulafungin	
Hematologic	Neutropenia		1.2%	
	Leukopenia		0.9%	
	Eosinophilia	3%	Rarely related to infusion	
	Thrombocytopenia	<4%		
Gastrointestinal	Leukopenia	<4%		
	Decreased Hgb, Hct	3%–12%		
	Nausea	<3%	2.4%	1.0%
	Diarrhea		2.1%	
	Vomiting	<3%		0.7%
Miscellaneous	Dyspepsia		0.3%	
	Hyperbilirubinemia		3.3%	
	Increased GGT			<1%
	Elevated AST/ALT	Do not exceed 5X ULN, transient, reversible. ~14%, <2%, 11%–24%	Rare, and generally insignificant	<1%
	Hypokalemia	11% after 70 mg dose; <4% with 50 mg dose	1.8%	2.4%–3.1%
	Rash			<1%
	Pyrexia	12%–26%, 3.6% (depending on comparator)		0.7%
	Headache	<3%		1.3%
	Flushing	<3%		
	Phlebitis/thrombophlebitis	3.5%, 12%–18%	Rare	1.3%
Infusion related reactions/ Histamine release	2%	Rare	1 pt “flushing” with infusion	

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutaryl transferase; Hct, hematocrit; Hgb, hemoglobin; pt, patient; ULN, upper limit of normal.

interaction may be overstated. Three retrospective analyses of the use of caspofungin and cyclosporine in patients do not support a risk of clinically relevant hepatotoxicity (Marr, Hachem et al 2004; Sanz-Rodriguez et al 2004; Glasmacher et al 2006). A recent study further illustrates the lack of clinical significance of caspofungin-immunosuppressant interactions. Sixty-six patients from Phase II and III clinical trials received caspofungin in combination with cyclosporine (6 patients, for a mean of 14 days), tacrolimus (58 patients, 21 days), sirolimus (3 patients, 12 days), and mycophenolate (22 patients, 28 days). No patient on cyclosporine developed increased transaminases or discontinued therapy with caspofungin due to an adverse event. Two patients receiving sirolimus experienced transaminase elevations >2.5 times the ULN, and the incidence of transaminase elevations in the caspofungin-tacrolimus group was similar to the comparator agent combination (amphotericin B plus tacrolimus) (Kartsonis, Lipka, et al 2005).

One case report describes severe thrombocytopenia associated with caspofungin use in a patient with multiple

aortic valve vegetations. The patient was receiving several agents known to cause thrombocytopenia, including piperacillin-tazobactam, heparin, 5-flucytosine, and amphotericin B deoxycholate; however, the time course (and subsequent rechallenges with several agents) were most consistent with caspofungin. However, the authors do not discuss the possible effects that the patient’s significant disease processes and comorbidities may have had on platelet counts. Nevertheless, the caspofungin package insert cites the incidence of decreased platelet counts to be 3.1% and 1.5% in patients receiving doses of 50 mg and 70 mg daily, respectively (Lynch and Wong-Beringer 2004).

It appears from clinical trials that caspofungin may have a higher propensity for causing histamine-induced reactions compared with other echinocandins (Table 2). These reactions may manifest as rash, facial swelling, pruritus, facial swelling, sensation of warmth, and/or bronchospasm (see http://www.cancidas.com/caspofungin_acetate/cancidas/hcp/product_highlights/tolerability/index.jsp). However, the package insert for micafungin states that patients may experience more frequent histamine-mediated

reactions when the drug is infused more rapidly than 1 hour (Micafungin PI 2005). Possible histamine-mediated symptoms are infrequent when anidulafungin infusion rates do not exceed 1.1 mg/minute. However, more experience and comparative trials are needed to adequately assess the relative incidence for each agent.

It appears that certain structural alterations in the core molecule (ie, cyclic hexapeptides) of the echinocandins influence their ability to influence histamine release. Specifically, compounds with high proximal positive charge density demonstrated a high histamine-releasing potency when measured in mouse models with a histamine-radioligand-immunoassay (Wang et al 2003). In vitro studies in which human mononuclear, mast, and peripheral blood cells were incubated with caspofungin demonstrated a significant increase in histamine when incubated with peripheral and mast cells. Likewise, the activity of histamine N-methyltransferase, an enzyme which degrades histamine, was reduced by 33% in peripheral blood. Anidulafungin and micafungin were not studied in this in vitro system (Cleary et al 2003).

Comparison of echinocandins by indication

Clinical trials

Febrile neutropenia

Caspofungin

To date, only caspofungin has been studied for empiric therapy in patients with febrile neutropenia; caspofungin received FDA approval for this indication based on the results of a noninferiority study in 1095 patients. These high-risk patients (~60% in both groups had a primary diagnosis of acute myelogenous leukemia) were randomized to receive infusions of either caspofungin (70 mg loading dose, followed by maintenance doses of 50 mg every 24 hours for a median of about 10 days) or liposomal amphotericin B (3.0 mg/kg of body weight). Of those receiving caspofungin and amphotericin B, respectively, 190/556 (33.9%) and 180/539 (33.7%) patients had a favorable response, defined as a composite score of 5 criteria: successful treatment of baseline fungal infection; absence of breakthrough fungal infection during therapy or within 7 days after the end of therapy; survival for 7 days after discontinuation of therapy; resolution of fever; and no premature discontinuation of drug due to lack of efficacy or toxicity. Overall, outcomes with caspofungin therapy were equivalent to therapy with liposomal amphotericin B.

However, secondary analysis suggested that therapy with caspofungin therapy was significantly more successful than liposomal amphotericin B in the treatment of baseline infections: 14/27 (51.9%) versus 7/27 (25.9%), respectively, and resulted in a higher proportion of patients surviving at least 7 days. Liposomal amphotericin therapy was associated with a significantly higher rate of adverse drug reactions, including nephrotoxicity and infusion-related events (Walsh et al 2004).

Prophylaxis in hematopoietic stem cell transplantation and high-risk patient populations

The incidence of invasive fungal infections in patients receiving hematopoietic stem cell transplantation (HSCT) is between 14% and 25%; these infections are associated with a high rate of mortality (Lin et al 2001; Wisplinghoff et al 2004). Numerous studies have examined the utility of antifungal agents in preventing invasive infection (Hamza et al 2004). Although fluconazole is FDA-approved for this indication, it lacks clinical activity against *C. krusei* and *Aspergillus* spp. (Diflucan PI 2004). Potential advantages of echinocandins versus fluconazole for this indication include their expanded spectrum of activity against *Candida* species and *Aspergillus*, and their decreased potential for drug interactions. Potential disadvantages include their higher cost, lack of oral formulations, and lack of activity against emerging pathogens such as *Scedosporium*, *Fusarium*, and zygomycetes.

Caspofungin

Recently, caspofungin has been evaluated as prophylaxis in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. Intravenous caspofungin (50 mg daily) was compared with intravenous itraconazole (200 mg twice daily X 2 days, then 200 mg once daily). Success of therapy was defined as completion of prophylaxis (which was continued until any of the following: absolute neutrophil count >500 for 2 consecutive days; complete response; death; change in leukemia therapy; unacceptable toxicity; proven or probable invasive fungal infection; or 35 days of prophylaxis) without development of invasive fungal infection during the period of prophylaxis. The median length of prophylaxis was 21 days in both groups. Prophylaxis was effective in 44/86 (51%) of patients in the itraconazole group and 55/106 (52%) in the caspofungin group. Twelve patients developed invasive fungal infections: 5 in the itraconazole group (one patient with *Aspergillus* pneumonia and four patients with candidemia- one due to

C. krusei, one due to *C. albicans*, and two due to *C. glabrata*) and 7 in the caspofungin group (2 patients with disseminated *Trichosporon* infection, two with *Aspergillus* pneumonia, one with *Fusarium* cellulitis, one with candidemia due to *C. parapsilosis*, and one with both candidemia due to *C. albicans* and *C. glabrata* and concurrent *Aspergillus* pneumonia). Mortality was similar in both groups. This study illustrates the disappointing efficacy of fungal prophylaxis in high-risk patients and how prophylaxis may enable organisms that are not susceptible to the prophylactic antifungal agent to cause infection (Mattiuzzi et al 2006).

Micafungin

van Burik and colleagues (2004) evaluated 882 adult and pediatric patients who had undergone allogeneic (for any indication) or autologous (for hematological malignancy) HSCT. Patients were randomized to receive infusions of either micafungin 50 mg daily or intravenous fluconazole 400 mg daily until the earliest of the following: ≤ 5 days after engraftment; day 42 after HSCT; the development of proven, probable, or suspected invasive fungal infection; the development of unacceptable drug toxicity; death; or withdrawal or discontinuation from study participation. Overall treatment success (defined as the absence of proven, probable, or suspected fungal infection throughout the period of prophylaxis, and through the end of a 4-week post-treatment period) was 80% in the micafungin arm, and 73.5% in the fluconazole arm. Breakthrough infections during prophylaxis included 1 case each of *C. albicans*, *C. parapsilosis*, and *C. lusitaniae* during micafungin therapy; following fluconazole therapy 1 case each of *C. krusei* and *C. parapsilosis* were observed. There was 1 case of probable aspergillosis and one case of fusariosis in the micafungin treatment arm, and 7 cases (4 proven and 3 probable) of aspergillosis among patients treated with fluconazole ($p=0.071$). The only episode of zygomycosis occurred in a patient treated with micafungin. Significantly fewer patients in the micafungin arm 64/425 (15%) versus the fluconazole arm 98/457 (21%) required empiric antifungal therapy. Mortality was decreased, although not significantly, in the micafungin arm (5.7% vs 4.2%, respectively). Based on this limited data, micafungin may provide an option for prophylaxis in patients undergoing HSCT (van Burik et al 2004).

The two available studies examining the efficacy of echinocandins in preventing infections in high-risk patients demonstrated remarkably different results. The micafungin study included significantly more patients, and achieved

relatively high rates of successful outcomes (possibly due to the extremely high-risk patient population in the caspofungin group) compared with the caspofungin study. As such, it is difficult to directly compare the two agents. However, it does appear that both caspofungin and micafungin would be acceptable options in the prophylaxis of fungal infections in high-risk patients.

An important limitation of the study is that the duration of prophylaxis was too short to evaluate efficacy in the late post-engraftment period in allogeneic transplant recipients, when this population is at often at increased risk for invasive aspergillosis due to the use of corticosteroids, or the presence of graft-versus-host disease (GVHD) or cytomegalovirus (CMV) infection.

Invasive aspergillosis

Much of the data concerning the use of echinocandins in invasive aspergillosis is derived from trials using combinations of antifungal agents (discussed in more detail below). However, both caspofungin and micafungin have been studied as single-agent therapy in patients with invasive aspergillosis.

Caspofungin

Maertens and colleagues (2004) evaluated the use of intravenous caspofungin (administered as a 70 mg loading dose on the first day, then 50 mg daily) in patients refractory to (86%) or intolerant of (14%) previous antifungal therapy. Response was determined by a panel of 3 experts in fungal infections. A "complete response" was defined as resolution of all signs, symptoms, and radiographic evidence of aspergillosis, while a "partial response" was defined as "clinically meaningful improvement" in the above characteristics. Overall, 37/83 (45%) patients had a favorable response (complete + partial). Of the patients intolerant to previous therapy, 9/12 (75%) had a favorable response, while 28/71 (39.4%) of those refractory to previous therapy responded (1/3 were refractory to >1 drug).

In a second, compassionate-use study, caspofungin was assessed in an additional 48 patients (of whom 3 were not evaluated at the end of therapy) with aspergillosis refractory to or intolerant of other therapy. An overall favorable response (using the same criteria as the previous study) was observed in 20/45 (44%) patients, with 9/45 (20%) exhibiting a complete response to therapy. Of 10 patients who received caspofungin in conjunction with another antifungal agent, only 1 patient survived, highlighting the severity of infection in these patients (Kartsonis, Saah, et al 2005).

There are limited data assessing caspofungin as first-line therapy in patients with proven (7/32 [22%]) or possible (25/32 [78%]) aspergillosis. An overall response rate of 18/32 (56%) was observed. Of the 18 responders, 12 (66%) experienced complete and 6 (33%) partial responses. Twelve of the 32 patients (38%) did not respond and 7 died of mycotic infection. All patients who were neutropenic received G-CSF therapy. Interestingly, 2/6 patients who did not respond to caspofungin responded to voriconazole therapy, and 6/6 of those with a partial or stable response to caspofungin responded to voriconazole (Candoni et al 2005).

Additional case reports have corroborated the utility of caspofungin in a diverse group of infections and patient populations, including invasive fungal infections in immunocompromised hosts (Taccone et al 2003; Carby et al 2004; Ifran et al 2004). Several unique cases have shown promising results: subcutaneously disseminated aspergillosis in an allogeneic stem cell transplant patient, *Aspergillus* brain abscess in a diabetic patient, cerebral aspergillosis treated with amphotericin B deoxycholate plus caspofungin, and 3 patients with endophthalmitis treated with voriconazole + caspofungin (Chameuleau 2003; Colombo and Rosas 2003; Breit et al 2005; Ehrmann et al 2005). There have also been reports of treatment failures with caspofungin. In one, a renal transplant patient treated with voriconazole and caspofungin for pulmonary aspergillosis developed infection due to *Rhizopus oryzae*, the patient passed away after less than one week of treatment with liposomal amphotericin B. In another case, an HSCT patient who developed pulmonary aspergillosis failed long-term treatment with varied combinations of liposomal amphotericin B, itraconazole, and caspofungin, but resolved following 7 months of voriconazole therapy (Blin et al 2004; Eibl et al 2004).

Micafungin

Clinical data regarding the use of micafungin for the treatment of aspergillosis is expanding. Administration of intravenous micafungin 300 mg daily for 50 days was successful in the treatment of pulmonary infection with *A. fumigatus* in a patient with acute myeloid leukemia who had required repeated and prolonged courses of intravenous amphotericin B deoxycholate 1 mg/kg/day (Yokote et al 2004). In another case, a patient with acute lymphoblastic leukemia complicated by invasive pulmonary aspergillosis responded to 75–150 mg daily of intravenous micafungin. The higher dose resulted in increased serum concentrations

of micafungin, and was associated with improvement in signs and symptoms of infection (Ota et al 2004). A Phase II study in Japan enrolled patients with presumed or documented infection due to *Aspergillus* or *Candida* spp. Patients received intravenous micafungin at doses of 25–150 mg daily for 13–56 days. Response was defined as improvement in radiologic findings without clinical deterioration for invasive pulmonary aspergillosis (IPA); as improvement in both parameters for patients with chronic necrotizing pulmonary aspergillosis (CNPA); and as either radiologic improvement without clinical decline, or clinical improvement without radiologic decline, in patients with pulmonary aspergilloma (PA). Overall, 24/41 (59%) patients responded: 6/10 with IPA, 6/9 with CNPA, and 12/22 with PA (Kohno et al 2004). In a recent, open-label, noncomparative, international study in 225 adult and pediatric patients (of whom 66 (29%) were neutropenic at baseline) the use of intravenous micafungin was evaluated in 29 (13%), as primary therapy, and in 192 (85%) patients refractory to, or in 4 (2%) intolerant to previous antifungal therapy. The dosage of micafungin was 75 mg/day initially (1.5 mg/kg/day in patients ≤ 40 kg); the dosage was increased in increments of 75 mg/day (1.5 mg/kg/day in patients ≤ 40 kg) if cultures remained positive, progression of disease was evident, or no improvement was observed. Response was determined by a panel of 3 experts in fungal infections. The mean daily dose in adults was 111 mg/day (median 97 mg/day). The mean duration of treatment was 54 days. Of 96 patients whose doses were not escalated, 30 (31%) had a favorable response. Of 192 refractory patients, 148 (77%) had received a lipid preparation of amphotericin B, 86 (45%) amphotericin B deoxycholate, 66 (34%) itraconazole, 7 (4%) caspofungin, 5 (3%) voriconazole, and 5 (3%) posaconazole. Combination therapy (micafungin added to previous failing therapy) was utilized in 191 patients. Overall, 80 (36%) of patients had a favorable (complete + partial) response; and additional 25 (11%) of patients experienced stabilization of their infection. Of 29 patients who received micafungin as primary therapy, 11 had a favorable response (5/17 of those receiving combination therapy and 6/12 of those receiving micafungin alone). In the 34 patients receiving micafungin alone (18 refractory, 12 as primary therapy, and 4 due to prior drug toxicity), 15 (44%) had a favorable response (Denning et al 2006). This study, very similar to the study by Maertens and colleagues with caspofungin, suggests that micafungin has clinical efficacy similar to that of caspofungin in the treatment of invasive aspergillosis.

Micafungin has also been studied in pediatric patients (<16 years old) with proven or probable invasive aspergillosis. In a noncomparative study, 58 patients (4 newly diagnosed, 54 refractory to prior therapy of whom 43% had undergone an allogeneic bone marrow transplant, and 47% had undergone chemotherapy) with a mean age of 9 ± 4 years were treated with an initial dose of 1.5 mg/kg/day of micafungin; 30 patients received further dose escalation, and the mean treatment dose was 2.0 ± 1.2 mg/kg/day. Only 2 patients received micafungin alone, while the others received combination therapy with other antifungals (the majority, 47, receiving liposomal amphotericin B). Overall response (complete + partial) was obtained in 26/58 (45%) patients. Of these, 9 (16%) had a complete response, and 17 (29%) had a partial response. 5/21 (24%) of those infected with *A. fumigatus* and 11/20 (55%) with *A. flavus* responded. These response rates are similar to those of the trials described above, and as such, micafungin (especially in combination) is an option for the treatment of invasive aspergillosis in pediatric patients (Flynn et al 2006).

Despite the available data encompassing very low numbers of patients, the above studies are still significant indicators of efficacy in a devastating disease. As evidence of this, caspofungin received FDA approval for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies based solely on the results of the Maertens study (83 patients!). The 2 studies evaluating the use of echinocandins as first-line therapy for invasive aspergillosis are interesting, and demonstrate similar responses for caspofungin and micafungin. Possibly the most urgent need for additional data is in clinical trials examining the use of the echinocandins in the first-line or combination therapy of invasive aspergillosis.

Esophageal candidiasis

Caspofungin and micafungin have been studied extensively, and anidulafungin, less extensively, in patients with esophageal candidiasis.

Caspofungin

Intravenous doses of caspofungin (35 mg, 50 mg, or 70 mg daily) were compared with intravenous fluconazole 200 mg daily or amphotericin B 0.5 mg/kg/d for the treatment of clinically or microbiologically fluconazole-resistant *Candida* esophagitis. Of 31 patients, 14 (45%) were refractory to fluconazole and 17 (55%) had fluconazole MICs of ≥ 16 μ g/mL. Overall, 7/11 (64%) of fluconazole-

refractory patients treated with caspofungin responded, and 11/14 patients (79%) whose *Candida* isolates had decreased susceptibility to fluconazole (including 5/6 (83%) patients with fluconazole MICs ≥ 64 μ g/mL) treated with caspofungin responded (Kartsonis et al 2002).

In a compassionate-use study with caspofungin in 21 patients with invasive mucosal candidiasis (17 esophageal, 4 oropharyngeal), 19 (91%) of whom had HIV disease and were refractory to other therapy, 18/21 (86%) of patients had a favorable response (Kartsonis et al 2004). A subsequent study analyzed 120 patients with endoscopically and microbiologically documented esophageal candidiasis from 4 phase II/III caspofungin trials; *C. albicans* was isolated in 109/110 of isolates, and was the sole isolate in 77%. Caspofungin (50 mg daily) was administered for a median of 12 days in 120 patients. Symptoms resolved in 117/123 (95%) patients, within a median of 4 days. Response rates were not significantly different for patients with CD4 counts greater than or less than 50 cells/mm³. However, 17% of patients experienced relapse within 2 weeks of discontinuation of therapy (Dinubile et al 2002).

Following these studies, in a randomized, double-blind study comparing intravenous therapy with fluconazole (200 mg daily) with caspofungin (50 mg daily) once daily for 7 to 21 days, no significant difference in favorable response rates (66/81 [81%] versus 80/94 [85%] patients, respectively), were observed. Symptoms resolved by the fifth day of treatment in the majority of patients. Relapse was observed within 4 weeks following discontinuation of therapy in 12/72 (17%) and 18/64 (28%) of patients receiving fluconazole and caspofungin, respectively (Villanueva et al 2002).

Intravenous therapy for 2 weeks with caspofungin (50 mg or 70 mg daily) was compared with amphotericin B deoxycholate 0.5 mg/kg/day in 122 patients with oropharyngeal or esophageal candidiasis, the majority of whom were HIV-infected. Patients with possible fluconazole resistance were excluded. The median time to symptom resolution (4 days) was similar in all groups. Endoscopic success was achieved in 74%, 89%, and 63% in patients treated with caspofungin 50 mg, 70 mg, and amphotericin B, respectively, at the 14-day post-treatment follow-up. Significantly more adverse events occurred in the amphotericin B arm, although only 1 was deemed serious. Interestingly, the authors found no appreciable increases in adverse events between the 2 doses of caspofungin which showcases the future possibility of a valuable option of increasing doses in non-responders without expectation of

a higher rate of side effects (Villanueva et al 2001). In a similar study, intravenous caspofungin (35 mg, 50 mg, or 70 mg daily) or conventional amphotericin B (0.5 mg/kg of body weight once daily) were administered for 7 to 14 days. A modestly higher proportion of patients in each of the caspofungin groups (74% to 91%) achieved favorable responses compared with amphotericin B recipients (63%); however, there was considerable overlap in the 95% confidence intervals surrounding these point estimates (Arathoon et al 2002).

Micafungin

Micafungin was studied in 120 South African patients with HIV-related esophageal candidiasis: groups of 20 patients were randomized to one of 6 dosing regimens (12.5 mg, 25 mg, 50 mg, 75 mg, or 100 mg per day). Clinical response was found to be dose dependent: 6/18 (33.3%) of patients in the 12.5 mg daily dosage group experienced clinical clearing, compared with 18/19 (94.7%) of patients in the 100 mg daily dosage group. In addition, all patients at dose schemes of 50 mg or greater exhibited endoscopic improvement. Of concern, only 84 patients were included in the per-protocol analysis, as 13 patients discontinued therapy due to adverse events, and 16 patients were excluded due to a negative histology or cytology, thus signifying a lack of firm diagnosis. Despite this, most adverse events were considered mild to moderate, consisting mostly of gastrointestinal disturbances, liver function test abnormalities, and rash (Pettengell 2004).

A double-blind, randomized, noninferiority study compared response rates of micafungin (intravenous doses of 50 mg, 100 mg, or 150 mg/daily) with intravenous fluconazole (200 mg) for 14–21 days in 245 adult HIV-positive patients. Once again, a dose-dependent response was shown for micafungin, with a 69% documented cure in the 50 mg arm and 90% cure in the 150 mg arm. Fluconazole exhibited a 87% success rate. Based on these findings, micafungin was determined to be noninferior to fluconazole when administered at doses of 100 mg and 150 mg. 50% of patients had improvement by 3 days of treatment, and 75% were improved by day 7 (de Wet et al 2004).

Finally, a randomized, double-blind, noninferiority study compared a minimum of 14 days of therapy with intravenous micafungin 150 mg daily with intravenous fluconazole 200 mg daily. As expected, the majority of patients had a diagnosis of HIV (94%), and *C. albicans* was most often implicated as the cause of infection (98%). The mean number of days on study medication was similar for both groups

(about 14 days), as were the rates of endoscopic cure (87.7% for micafungin, 88.0% for fluconazole), and clinical success (94.2% and 94.6%, respectively). Again, improvement was often discernible within 3–5 days, and the rate of relapse was higher, although not significantly so, in the micafungin arm (15.2% vs 11.3% through week 4) (de Wet et al 2005).

In a recent multicenter, multinational, double-blind, randomized, noninferiority study in 452 patients with esophageal candidiasis, alternate day dosing of intravenous 300 mg of micafungin was as effective as daily intravenous doses of either 150 mg of micafungin or 50 mg of caspofungin (Buell et al 2005).

Anidulafungin

In a randomized, double-blind, noninferiority study in 601 patients, anidulafungin (100 mg intravenously on day 1 followed by 50 mg daily thereafter) was comparable to oral fluconazole (200 mg on day 1, 100 mg daily thereafter) for the treatment of esophageal candidiasis. The rates of endoscopically-confirmed success were 98.8% and 97.2% for fluconazole and anidulafungin, respectively. Of concern, a 2-week follow-up revealed that only 64.4% of patients in the anidulafungin group compared with 89.5% of patients taking fluconazole had sustained success. This may have been compounded, however, by the finding that more patients took antiretrovirals during treatment in the fluconazole arm (Krause, Simjee, et al 2004).

Summary

Based on currently available literature, there are no clear distinctions between the echinocandins when used in the treatment of esophageal candidiasis. All 3 agents have proven noninferior to the current standard of care (fluconazole), and all 3 carry a concern of significant relapse/reinfection rates. In rabbits, poor penetration of anidulafungin into saliva (although penetration into esophageal tissue was quite high) has been demonstrated; whether this is true for other echinocandins or in humans is not known (Petraitis et al 2001). Until a comparative class study is available, no clear distinction is evident based on clinical efficacy.

Invasive candidiasis

Caspofungin

Caspofungin has been studied extensively in patients with invasive candidiasis. Prior to its licensure, caspofungin was evaluated in 16 patients with invasive candidiasis who were refractory to or intolerant of other antifungal therapy: 8/16

(50%) of the patients had acute leukemia/lymphoma, and 5/16 (31%) were diabetic. Sites of infection were widespread, including four patients with chronic disseminated disease. A favorable response was observed in 13/15 patients (one patient died of staphylococcal sepsis prior to evaluation) (Kartsonis, Killar, et al 2005). Following this, a randomized, double-blind trial compared caspofungin (50 mg daily) with amphotericin B deoxycholate (0.6–0.7 mg/kg/day) in 239 patients with invasive candidiasis. A successful outcome was achieved in 73.9% and 61.7% of patients receiving caspofungin and amphotericin B, respectively (95.6% Confidence Interval [CI]: -0.7 to 26.0); response rates were consistent across most infection sources, including 7 patients with *Candida* endophthalmitis. Mortality was similar with either therapy (34.2% with caspofungin, 30.4% with amphotericin B) (Mora-Duarte et al 2002). These findings led to the subsequent FDA approval of caspofungin for this indication.

Several case reports have highlighted the use of intravenous caspofungin for uncommon or off-label indications. One case documents resolution of non-*albicans* *Candida* endocarditis without valve replacement, using a 70 mg loading dose followed by 50 mg daily for 6 weeks. The only other antifungal agent the patient had received was intravenous fluconazole for 4 days prior to initiation of caspofungin (Rajendram et al 2005). In another case, a patient with endocarditis due to *C. guilliermondii* was cured with surgery and 6 weeks of caspofungin monotherapy (50 mg daily) (Nevado et al 2005). These two cases present an encouraging picture for the use of caspofungin, even as monotherapy, for the treatment of fungal endocarditis. A combination of liposomal amphotericin B and caspofungin was successful in treating a case of *Candida* endocarditis without valve replacement (Jimenez-Exposito et al 2004). However, another patient with *C. albicans* endocarditis did not respond to caspofungin monotherapy and surgery, and developed likely fungal brain abscesses. The patient subsequently improved on liposomal amphotericin B + oral fluconazole therapy. This study highlighted concerns that the poor central nervous system (CNS) penetration of caspofungin might allow for dissemination of fungi to the CNS (Prabhu and Orenstein 2004). However, in another case report, a patient with *C. albicans* meningitis refractory to amphotericin B (1 mg/kg/day), intravenous fluconazole and intrathecal amphotericin B (1 ml of 0.25 mg/ml 3 times per week) improved dramatically following caspofungin monotherapy (Liu et al 2004). Finally, 2 case reports present conflicting data concerning the use of caspofungin in the

treatment of *Candida* endophthalmitis. In one case, a patient failing caspofungin monotherapy had undetectable intravitreal concentrations of caspofungin; the patient was subsequently cured after therapy with amphotericin B lipid complex (5 mg/kg/day) (Gauthier et al 2005). However, another patient was cured after a 28-day course of caspofungin monotherapy (initially 50 mg daily, later decreased to 35 mg daily due to moderate hepatic impairment). Intravitreal drug concentrations of caspofungin were not obtained (Sarría et al 2005). These case reports are interesting, but do not provide sufficient data upon which to form decisive conclusions regarding the use of caspofungin in endocarditis, meningitis, and endophthalmitis.

There are limited data regarding the use of caspofungin monotherapy in pediatric patients with invasive candidiasis. Encouraging results were observed when caspofungin was substituted for amphotericin B deoxycholate in 9 neonates with persistent infection. All blood cultures were sterilized within 3 to 7 days of initiating caspofungin, and in one case, an atrial vegetation was eradicated (Odio et al 2004). Another case report also documents a successful use of caspofungin in a patient with amphotericin B- and fluconazole-resistant *Candida glabrata* endocarditis (Mrowczynski and Wojtalik 2004). Caspofungin has also been added without serious side effects to failing regimens in a variety of pediatric patients, including a low-birth-weight neonate, several bone marrow transplant recipients, and a 3-year old child with persistent candidemia, with generally positive results (Franklin et al 2003; Hesselting et al 2003; Castagnola et al 2004; Wertz and Pretzlaff 2004).

Micafungin

Data regarding the efficacy of micafungin for the treatment of invasive candidiasis are emerging. An open-label study in Japan documented a 100% response (6/6 patients) in the treatment of candidemia. However, one patient with disseminated candidiasis did not respond to treatment (Kohno et al 2004). In an open-label, noncomparative trial in 126 patients with candidemia, micafungin therapy produced a complete or partial response in 83.3% of patients; however, since dose escalation (with dosages up to 200 mg/day) was allowed, and the majority of patients received concurrent antifungal agents, the clinical applicability of this trial is limited (Ostrosky-Zeichner et al 2005). A double-blind, noninferiority study comparing intravenous

micafungin (100 mg daily) with liposomal amphotericin B (3 mg/kg/day) for 2-4 weeks was undertaken in mainly non-neutropenic (12.9% vs 10.5% of patients, respectively), mostly candidemic (~85% in both arms) patients. Micafungin treatment was considered effective (clinical plus mycological response) in 89.6% of patients (181/202) compared with 89.5% (170/190) in the amphotericin B group. 62.4% and 58.9% of patients, respectively, were infected with non-*albicans* *Candida* species. Both groups were equal with regard to eradication of *C. glabrata* and *C. parapsilosis*, and catheters were removed in an equal frequency in both groups. The amphotericin B group had a significantly higher incidence of side effects, including infusion-related reactions and increases in serum creatinine. As such, the investigators concluded that micafungin was noninferior to amphotericin B, but displayed a significantly more favorable side effect profile (Ruhnke et al 2005). A randomized, 1:1:1, double blind, noninferiority trial comparing 2 doses of micafungin (100 mg/day and 150 mg/day) with caspofungin (70 mg loading dose, then 50 mg/day) was recently presented in abstract form. The primary efficacy endpoint was clinical and microbiological response at the end of intravenous therapy, with a pre-specified margin for noninferiority of -15%. 593 patients received at least one dose of study drug, and the three groups had similar baseline characteristics. Overall success was 73.9% for micafungin 100 mg/day, 70.3% for micafungin 150 mg/day, and 71.4% for caspofungin. Based on these results, micafungin was determined noninferior to caspofungin. In addition, this study showed no advantage of micafungin at 150 mg/day compared with 100 mg/day. The safety profiles for the 3 treatments were similar. Further analysis of response stratified by organism are pending (Betts et al 2006).

Micafungin (2 mg/kg/day) was recently compared with liposomal amphotericin B (3 mg/kg/day) for the treatment of invasive candidiasis in pediatric patients (≤ 15 years old) in a randomized, double-blind study. The study included 98 patients: the majority had candidemia (92% in the micafungin group, 94% in the amphotericin B group), with 30 (63%) and 35 (70%) patients, respectively, infected with non-*albicans* species. Overall treatment success (clinical and mycological response) in the modified intention-to-treat patients was similar for the two agents, 35/48 (72.9%) for micafungin and 38/50 (76.0%) for amphotericin B. No significant differences were found when responses were analyzed according to patient age, neutropenic status, safety profiles, or in 12-week survival. As such, micafungin may

be considered in pediatric patients with candidiasis, especially those with candidemia (Arrieta et al 2006).

Anidulafungin

In a Phase II, dose-ranging study, 123 patients with invasive candidiasis were randomized to 50 mg, 75 mg, or 100 mg daily. Of the 68 evaluable patients (94% of which had candidemia only), success rates were 84%, 90%, and 89% in each group, respectively (Krause, Reinhardt, et al 2004). Eradication rates were also dose-dependent (74%, 85%, and 89%, respectively). MICs for both *C. albicans* and non-*albicans* isolates were similar, except for *C. parapsilosis* isolates, which comprised 9.5% of isolates. The MIC range (4–8 $\mu\text{g/mL}$) for this organism was significantly greater than those of other isolates. However, as described above with caspofungin, high MICs did not predict treatment failure: 6 of 7 infections due to isolates of *C. parapsilosis* with MICs of 4–8 $\mu\text{g/mL}$ were eradicated (Pfaller, Diekema, et al 2005). Based on these results, a randomized, double-blind Phase III trial compared intravenous anidulafungin (200 mg loading dose X 1, then 100 mg daily) with intravenous fluconazole (800 mg loading dose X 1, then 400 mg daily) in 256 patients was conducted. Patients in either arm could switch to oral fluconazole after 10 days. Approximately 3% of patients were neutropenic, and 89% had only candidemia. About 40% of isolates were of non-*albicans* spp. in both arms. Treatment success required both a clinical and microbiological response. A statistically significantly greater response was found in the anidulafungin arm in the microbiological intent-to-treat arm at the end of intravenous therapy (75.6% vs 60.2%). At the same time point, 6.3% of patients in the anidulafungin arm had persistence of infection, compared with 14.4% in the fluconazole arm. A secondary analysis at a two-week follow-up again revealed statistical superiority in the anidulafungin arm (64.6% vs 49.2%), with similar results again at six weeks (55.9% vs 44.1%). A subset analysis revealed that anidulafungin retained its statistical superiority only in patients with APACHE II scores >20 (Reboli et al 2005).

Summary

At this time, the only distinction that can be drawn between the echinocandin agents and their utility in invasive candidiasis is that caspofungin and anidulafungin, to date, are the only agents to have FDA approval. However, based on limited information, micafungin also appears to be effective. As such, it is difficult to discern the preferred echinocandin for the treatment of invasive candidiasis.

Studies which directly compare the agents would help delineate any differences.

Combination therapy with echinocandins and other antifungal agents

The unique mechanism of action of the echinocandins has rekindled an interest in utilizing combination antifungal chemotherapy. Most examples of additive or synergistic effects make theoretical sense, such as flucytosine + amphotericin B in cryptococcal meningitis and rifampin or an aminoglycoside in combination with a β -lactam antibiotic for selected bacteria. In the same way, an echinocandin in combination with a polyene or azole antifungal makes theoretical sense, given the different mechanisms of action. However, a logical theory does not exclude the possibility for antagonism when two agents are combined. The various combinations have been tested against several fungi, including *Trichosporon asahii* in a murine model (Serena et al 2005), *Scedosporium* spp in vitro (Yustes and Guarro 2005), *Cryptococcus* spp. in vitro (Johnson et al 2004), and *Mucor* in a successful patient case (Spellberg et al 2005). Several extensive reviews have been published recently on combination therapy for fungal infection (Lewis and Kontoyiannis 2001; Johnson et al 2004; Baddley and Pappas 2005). The only randomized, blinded study evaluating the efficacy of combination therapy involves fluconazole versus

fluconazole + amphotericin B deoxycholate for candidemia. This study found a trend towards improved outcomes in the combination therapy group (Rex et al 2003). However, at the present, most interest concerning combination therapy lies in the treatment of aspergillosis, given the continued high mortality of these infections. The results of in vitro and animal studies for the most relevant fungi are summarized in Table 3.

Caspofungin

Several small series of patients have reported successful treatment of refractory infections with combinations of caspofungin and itraconazole, voriconazole, or lipid preparations of amphotericin B. One study retrospectively assessed the response of 48 patients with invasive aspergillosis who received combination therapy with liposomal amphotericin B and caspofungin in whom 17 (35%) had received combination therapy as initial therapy, while an additional 31 (65%) patients had progressive disease on liposomal amphotericin B alone. The overall response rate was 42% (22% in patients with documented infection, and 60% in those with possible infection). In those patients whose disease had progressed on liposomal amphotericin B monotherapy, the response rate was 18% and 57%, respectively. 5/13 (38%) patients with neutropenia persisting through the study period responded to

Table 3 Echinocandin-containing combination antifungal therapy (in vitro and animal data) (Johnson et al 2004)

Caspofungin	<i>Candida</i> spp.	In vitro combination with fluconazole yielded generally indifferent results, and showed potential benefit in an animal study.
	<i>Aspergillus</i> spp.	In vitro and animal combination with AmB and triazoles generally synergistic. Antagonism not seen. AmB + caspofungin + flucytosine shown to be synergistic against all tested isolates in vitro (Dannaoui et al 2004). Sulfmethoxazole combination synergistic in 29/31 isolates in vitro (Yekutieli et al 2004).
	Mucormycosis	Combination with AmB showed survival benefit in animal model (Spellberg et al 2005).
Micafungin	<i>Aspergillus</i> spp.	In in vitro and animal models, the combination of AmB and triazole antifungals was generally synergistic, and significantly decreased the EC ₉₀ of voriconazole against <i>A. fumigatus</i> and <i>A. terreus</i> , but not <i>A. flavus</i> (Heyn et al 2005; Lewis and Kontoyiannis 2005).
	<i>Candida</i> spp.	Voriconazole combination indifferent in 97% of isolates, most likely due to already low MICs with micafungin (Heyn et al 2005). Combination with amphotericin B required to eradicate <i>C. glabrata</i> infection in immunosuppressed mice (Olson et al 2005).
	<i>Scedosporium</i> spp. and <i>Fusarium solani</i>	Combination with voriconazole synergistic in 64% of isolates. Antagonism not noted (Heyn et al 2005).
Anidulafungin	<i>Aspergillus</i> spp.	In vitro combination with AmB was antagonistic in 5/26 strains. Combination with itraconazole + voriconazole generally showed synergy (Philip et al 2005).
	<i>Candida</i> spp.	In vitro combination with AmB, itraconazole, ketoconazole, itraconazole, and 5-fluorocytosine generally showed additivity or indifference. Antagonism noted in all strains of <i>C. tropicalis</i> with combination of ketoconazole and anidulafungin (Karlowsky et al 2006).

Abbreviations: AmB, amphotericin B; EC₉₀, effective concentration 90%.

combination therapy (Kontoyiannis et al 2003). In a similar study, which included 85 patients with progression of disease despite 72 hours of appropriate therapy, 33 (39%) patients demonstrated a complete or partial response. However, 13 patients received triple therapy (micafungin, amphotericin B, and an azole) (Ratanatharathorn et al 2002). Investigators from the University of Washington examined the outcomes of 47 patients who failed amphotericin B formulations and received voriconazole alone or in combination with caspofungin. Compared with single-agent therapy, combination therapy significantly improved 3-month survival and reduced mortality (Marr, Boeckh, et al 2004). Another study analyzed the efficacy of caspofungin combined with polyene formulations (16 patients), itraconazole (7), or voriconazole (30) in patients refractory to (87%) or intolerant of (13%) prior therapy, of whom 7 (13%) patients had disseminated infection, and 43 (81%) had pulmonary infections. The average duration of therapy was 31 days (range 1–196), with only 10 patients (19%) receiving therapy for <7 days. Efficacy, determined by an independent expert assessment, was achieved in 29/55 patients (55%) at the end of combination therapy, and 25/51 (49%) after 84 days of therapy. At the end of combination therapy, efficacy was achieved in 18/30 (60%) in the caspofungin–voriconazole group, compared with 3/7 (43%) in the caspofungin–itraconazole arm and 8/16 (50%) in the caspofungin–amphotericin B arm. Efficacy was similar in patients refractory to prior therapy (54%) and in those intolerant (57%), as well as in patients who were either neutropenic or non-neutropenic at study outset (57% vs 52%, respectively) (Maertens et al 2005).

Singh and colleagues (2006) compared a historical control group of 47 solid organ transplant recipients treated as primary therapy for aspergillosis with liposomal amphotericin B monotherapy from 1999–2002, to 40 patients treated from 2003–2005 with voriconazole plus caspofungin (Singh et al 2006). 90-day mortality was significantly lower in the combination therapy versus the monotherapy group (51% vs 67.5%, respectively). In addition, in transplant recipients with renal failure, and in those with *A. fumigatus* infection, combination therapy was independently associated with an improved 90-day survival. As such, voriconazole + caspofungin may be preferred in solid organ transplant patients with invasive aspergillosis (Singh et al 2006). However, the results do not prove the superiority of combination therapy, especially since a previous randomized, controlled trial proved the superiority of voriconazole to amphotericin B deoxycholate for

aspergillosis (Herbrecht et al 2002). However, the control group may have experienced other differences in medical management from the case group. As such, a prospective trial which compares combination therapy versus voriconazole monotherapy would be more telling. In addition, a more recent study of 146 patients, 32% of whom were solid organ transplant recipients, found that primary combination therapy did not affect mortality or rates of favorable response (Kubin et al 2006).

Micafungin

A recent study of 98 bone marrow transplant recipients with invasive aspergillosis shows similar findings with micafungin-containing combination therapy. Initial dosing of micafungin was 75 mg/day, with escalation to a mean dose of 105 ± 60 mg/day. Response (complete and partial) was seen in 25/98 (26%) patients, the majority (83) of whom were refractory to previous therapy (Kontoyiannis et al 2006).

Micafungin combination therapy has also been evaluated in a case series involving 6 patients with pulmonary aspergillosis (2 with probable infection). Patients received intravenous amphotericin B deoxycholate (0.8–1.5 mg/kg/day) and micafungin (150–300 mg daily) for 14–90 days. 4/6 patients showed response in both radiological and mycological studies. 5/6 were determined to have treatment success (determined by the occurrence of one or more of the following without deterioration in any criteria: complete or partial response in clinical symptoms, radiological findings, and mycological tests) (Miyazaki et al 2005).

Summary

To our knowledge, only one randomized clinical trial has evaluated combination therapy for the treatment of fungal infections (Rex et al 2003). In vitro and animal data are of especially limited use in invasive fungal diseases, due to the numerous patient-specific factors that greatly affect patient outcomes. In addition, the available clinical studies evaluating combination therapy are fraught with limitations and discrepancies. New studies have not rectified these issues, and add to a confusing mix of diverse disease states, drug combinations, and study designs. This has made the topic very controversial, and at this time, practice seems to be based more on preference and theory than on evidence. This is evidenced by the varied opinions of experts in the field (Chamolli and Kontoyannis 2006; Munoz et al 2006; Leather and Wingard 2006). Thus, firm recommendations regarding the use of combination therapy can not be given

at this time. However, based on the available evidence, it appears that the use of caspofungin in combination with either voriconazole or amphotericin B should be considered by clinicians in patients with *Aspergillus* infections refractory to single-agent therapy, or those with disseminated disease. This benefit, although not certain at this point, is logical, when one considers the mechanisms of action of the different antifungal agents, as well as caspofungin's proven efficacy in refractory aspergillosis. At this time, micafungin has shown similar trends in one trial and a case series, while anidulafungin has only been tested in vitro models. The evidence concerning combination therapy in infections due to other fungi is too limited to extrapolate clinically.

Dosage/administration

The dosages for the treatment of FDA-approved indications in adults are listed in Table 4. For all echinocandins, slow infusions (1 hour for caspofungin and micafungin, a rate ≤ 1 mg/minute for anidulafungin) are recommended. Pharmacokinetic data support the use of once daily intravenous dosages for all echinocandins. Micafungin is the sole echinocandin for which a loading dose is not recommended. In addition, optimal dosages of micafungin have not been established in either esophageal or systemic infections. Thus far, dosages for the treatment of esophageal candidiasis in HIV-infected patients have ranged from 50 mg to 150 mg daily, while dosages of up to 300 mg daily have been utilized for the treatment of invasive aspergillosis.

For all echinocandins, dosage adjustments are not required based on race, for the elderly, or for patients with severe renal dysfunction. Anidulafungin does not require any dose adjustment in patients with severe hepatic dysfunction, and micafungin does not require dosage adjustment in moderate dysfunction (has not been studied in severe dysfunction). The caspofungin maintenance dose, however, should be reduced to 35 mg daily in patients with moderate to severe hepatic dysfunction.

Availability

As of April 2006, caspofungin, micafungin, and anidulafungin are all FDA-approved in the US (Table 5). Caspofungin and micafungin are also available in Japan and Europe.

Summary

The echinocandins are important and exciting agents because of their novel mechanism of action, low incidence of serious adverse effects, and low potential for drug-drug interactions. As a class, they demonstrate potent activity against *Candida* spp., and are an option for the treatment of infections due to these organisms. In addition, caspofungin is a viable option for the treatment of refractory aspergillosis. Although micafungin is not FDA-approved for this indication, recent data suggests that it may also be effective. Likewise, caspofungin- or micafungin-containing combination therapy should be a consideration for the

Table 4 Adult dosing of echinocandins (Krause, Reinhardt, et al 2004; Cancidas PI 2005; Mycamine PI 2005; Reboli et al 2005; Ruhnke et al 2005; Eraxis PI 2006)

Indication	Dosage		
	Caspofungin (Cancidas®)	Micafungin (Mycamine®)	Anidulafungin (Eraxis®)
FDA approval (year)	January 2001	March 2005	February 2006
Empirical therapy for presumed fungal infections in febrile, neutropenic patients	70 mg LD 50 mg daily MD	-	-
Treatment of candidemia and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis, and pleural space infections	70 mg LD 50 mg daily MD	100 mg daily MD*	200 mg LD 100 mg daily MD
Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies	70 mg LD 50 mg daily MD	-	-
Treatment of patients with esophageal candidiasis	50 mg daily MD	150 mg daily MD	100 mg LD 50 mg daily MD
Prophylaxis of <i>Candida</i> infections in patients undergoing HSCT	-	50 mg daily MD	-

Note: *dosage used in clinical trial, however, not an FDA-approved dosage or indication

Abbreviations: FDA, Food and Drug Administration; LD, loading dose; MD, maintenance dose; HSCT, hematopoietic stem cell transplantation.

Table 5 Formulations of echinocandins (Cancidas PI 2005; Mycamine PI 2005; Eraxis PI 2006)

Agent (Brand name)	Formula Weight	Supply	Formulation	pH ¹	excipients	Administration	Incompatibilities	Storage ¹
casposungin (Cancidas [®])	1213.42	50 mg and 70 mg single use vials	Lyophilized white powder, ² freely soluble in water	6.6	sucrose, mannitol, acetic acid, NaOH	slow IV infusion over 1 hour	Dextrose	Final patient infusion solution in the IV bag or bottle can be stored at ≤25°C (≤77°F) for 24 hours or at 2 to 8°C (36 to 46°F) for 48 hours.
micafungin (Mycamine [®])	1292.26	50 mg vials	Lyophilized powder, ² freely soluble in water	5–7	Lactose, citric acid, NaOH	Reconstitute with 0.9% NaCl or 5% dextrose; slow IV infusion over 1 hour	NA	Stable for 24 hours at room temperature if protected from light
anidulafungin (Eraxis [®])	1140.3	50 mg vials	Lyophilized powder ² insoluble in water	NA	Fructose, mannitol, polysorbate 80, tartaric acid, NaOH or HCl	Reconstitute with 15 mL of 20% (w/w) dehydrated alcohol in water and further dilute with 0.9% NaCl or 5% dextrose; infuse at no more than 1.1 mg/minute	Compatibilities with medications or electrolytes NA	In refrigerator up to 24 hours

Note: ¹Final pH of reconstituted solution; ²for reconstitution.

Abbreviations: HCl, hydrochloric acid; IV, intravenous; NA, information not available; NaOH, sodium hydroxide.

treatment of severe infections due to *Aspergillus* spp.. Although the echinocandins share many common properties, data regarding their differences are emerging at a rapid pace. However, there continues to be a dire need for additional data concerning the echinocandins. Specifically, head-to-head comparison trials would help delineate differences between in vitro (theory) and in vivo clinical practice. More data are needed concerning echinocandin use as initial therapy for invasive aspergillosis. In addition, considering the substantial cost and somewhat theoretical benefit of combination therapy, controlled trials analyzing this use of echinocandins are desperately needed. Finally, continued data regarding the use of echinocandins for the treatment of unusual infections (meningitis, endophthalmitis, endocarditis, etc) would also help clarify the echinocandins' place in the antifungal armamentarium.

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