Echinocandin Antifungal Drugs in Fungal Infections
A Comparison

Sharon C.-A. Chen,[1] *Monica A. Slavin*[2] and *Tania C. Sorrell*[1]

1 Centre for Infectious Diseases and Microbiology, Westmead Hospital, and the University of Sydney, Westmead, New South Wales, Australia
2 Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Contents

Abstract

This review compares the pharmacology, spectrum of antifungal activity, pharmacokinetic and pharmacodynamic properties, safety and clinical efficacy of the three licensed echinocandins: caspofungin, micafungin and anidulafungin. Echinocandins inhibit the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall, and represent a valuable treatment option for fungal infections.

The echinocandins exhibit potent *in vitro* and *in vivo* fungicidal activity against *Candida* species, including azole-resistant pathogens. For all agents, strains with drug minimum inhibitory concentrations (MICs) of ≤2 μg/mL are considered susceptible; the MIC at which 90% of isolates tested were inhibited (MIC_{90}) values are typically <2 μg/mL but 100-fold higher MIC_{90} values are seen with *Candida parapsilosis* (1–2 μg/mL) and *Candida guilliermondii* (1–4 μg/mL). Activity is comparable between the three agents, although limited data indicate that anidulafungin may have low MICs against *C. parapsilosis* and *Candida glabrata* strains that demonstrate elevated MICs to caspofungin and micafungin. All three drugs have good fungistatic activity against *Aspergillus* spp., although minimal effective concentrations of micafungin and anidulfungin are 2- to 10-fold lower than those for caspofungin. Synergistic/additive *in vitro* effects of echinocandins when combined with a polyene or azole have been observed.

Clinical resistance to the echinocandins is rare despite case reports of caspofungin resistance in several *Candida* spp. Resistance has been attributed to mutations in the *FKS1* gene within two hot spot regions, leading to amino acid substitutions, mostly at position 645 (serine), yet not all *FKS1* mutants have caspofungin MICs of >2 μg/mL. Of the three echinocandins, the *in vitro* 'paradoxical effect' (increased growth at supra-MIC drug concentrations) is observed least often with anidulafungin.

All echinocandins have low oral bioavailability, and distribute well into tissues, but poorly into the CNS and eye. Anidulafungin is unique in that it undergoes elimination by chemical degradation in bile rather than via hepatic metabolism, has a lower maximum concentration and smaller steady state under the concentration-time curve but longer half-life than caspofungin or micafungin. In children, dosing should be based on body surface area. Daily doses of caspofungin (but not micafungin and anidulafungin) should be decreased (from 50 to 35 mg) in moderate liver insufficiency. All echinocandins display concentration-dependent fungicidal (for *Candida*) or fungistatic (for *Aspergillus*) activity. The postantifungal effect is 0.9–20 hours against *Candida* and <0.5 hours against *Aspergillus*. The echinocandins are well tolerated with few serious drug-drug interactions since they are not appreciable substrates, inhibitors or inducers of the cytochrome P450 or P-glycoprotein systems. In parallel with the greater clinical experience with caspofungin, this agent has a slightly higher potential for adverse effects/drug-drug interactions, with the least potential observed for anidulafungin. Caspofungin (but not micafungin or anidulafungin) dosing should be increased if coadministered with rifampicin and there are modest interactions of caspofungin with calcineurin inhibitors.

All three agents are approved for the treatment of oesophageal candidiasis, candidaemia and other select forms of invasive candidiasis. Only micafungin is licensed for antifungal prophylaxis in stem cell transplantation, whereas caspofungin is approved for empirical therapy of febrile neutropenia. Caspofungin has been evaluated in the salvage and primary therapy of invasive aspergillosis. Combination regimens incorporating an echinocandin showing promise in the treatment of aspergillosis. However, echinocandins remain expensive to use.

The incidence of systemic fungal infections continues to increase and new pathogens are emerging.[1-3] Epidemiological changes in the patterns of invasive fungal infections (IFIs) reflect not only the increasing population at risk but the emergence of antifungal-resistant fungal species. For example, there has been a worldwide shift in the species of *Candida* causing bloodstream infection away from *Candida albicans*;[1,4-6] this has implications for therapy since certain non-*albicans Candida* species, notably *Candida krusei* and *Candida glabrata*, are resistant or less susceptible to azole antifungal agents.[1]

For many years, amphotericin B was the only systemic antifungal agent for the treatment of IFIs. The advent of the triazoles and lipid amphotericin B formulations in the 1990s provided alternative therapeutic options. However, renal toxicity remains a major drawback of amphotericin B formulations, whilst drug interactions, hepatotoxicity and limitations to use in renal failure are primary concerns with newer-generation azoles.[7-9] In the last 5 years, a unique class of drug, the echinocandins, has been added to the antifungal armamentarium. The earliest lead compound (for anidulafungin) was identified in 1974, but it was not until 1989 that MK-0991 (caspofungin) was reported.[10] Caspofungin was approved in January 2001 by the US FDA for the treatment of IFIs in adults (July 2008 for use in children ≥3 months of age). Two more echinocandins, micafungin (approved March 2005) and anidulafungin (approved February 2006) have since been licensed for clinical use.[11-13] Caspofungin and anidulafungin are available worldwide, whilst micafungin is marketed in the EU, US, Japan and parts of Asia. The early promise of the echinocandins as effective anti-*Candida* and anti-*Aspergillus* agents has been supported by large clinical efficacy trials; these agents have had significant impact on the treatment of invasive candidiasis (IC) and invasive aspergillosis (IA).[14,15]

All the echinocandins have a similar spectrum of antifungal activity but have significant structural differences (figure 1), which may account for variations in their pharmacokinetics and drug interactions.[11-13] This article summarizes the pharmacology, pharmacokinetics, antifungal spectrum of activity, safety and clinical efficacy of the echinocandins in relation to their current therapeutic indications, highlighting the implications of similarities and differences between individual agents. Of particular clinical relevance is the exploration of maximal dosing limitations and drug-resistance mechanisms, and pursuit of an echinocandin-specific niche in combination therapy for treating invasive mould infections. Detailed descriptions of one or more specific aspects of the echinocandins can be found in recent publications.[17-24] We undertook an electronic search of, and critically evaluated, information on the pharmacology, pharmacokinetics, medicinal chemistry, *in vitro* and *in vivo* susceptibility, and clinical efficacy (from clinical trials, retrospective reviews and case series reports) of the echinocandins. Publications were accessed via PubMed (1990–July 2010) using the MEDLINE and EMBASE databases, using keywords that included 'echinocandins', 'caspofungin', 'micafungin', 'anidulafungin', 'fungal infections', 'invasive candidiasis', 'oesophageal candidiasis', '*Candida*', 'invasive aspergillosis', '*Aspergillus*', 'antifungal drugs', 'antifungal treatment', 'antifungal mechanism of action', 'antifungal susceptibility', 'clinical trials', 'pharmacokinetics', 'pharmacodynamics', 'antifungal resistance' and 'economic analysis'.

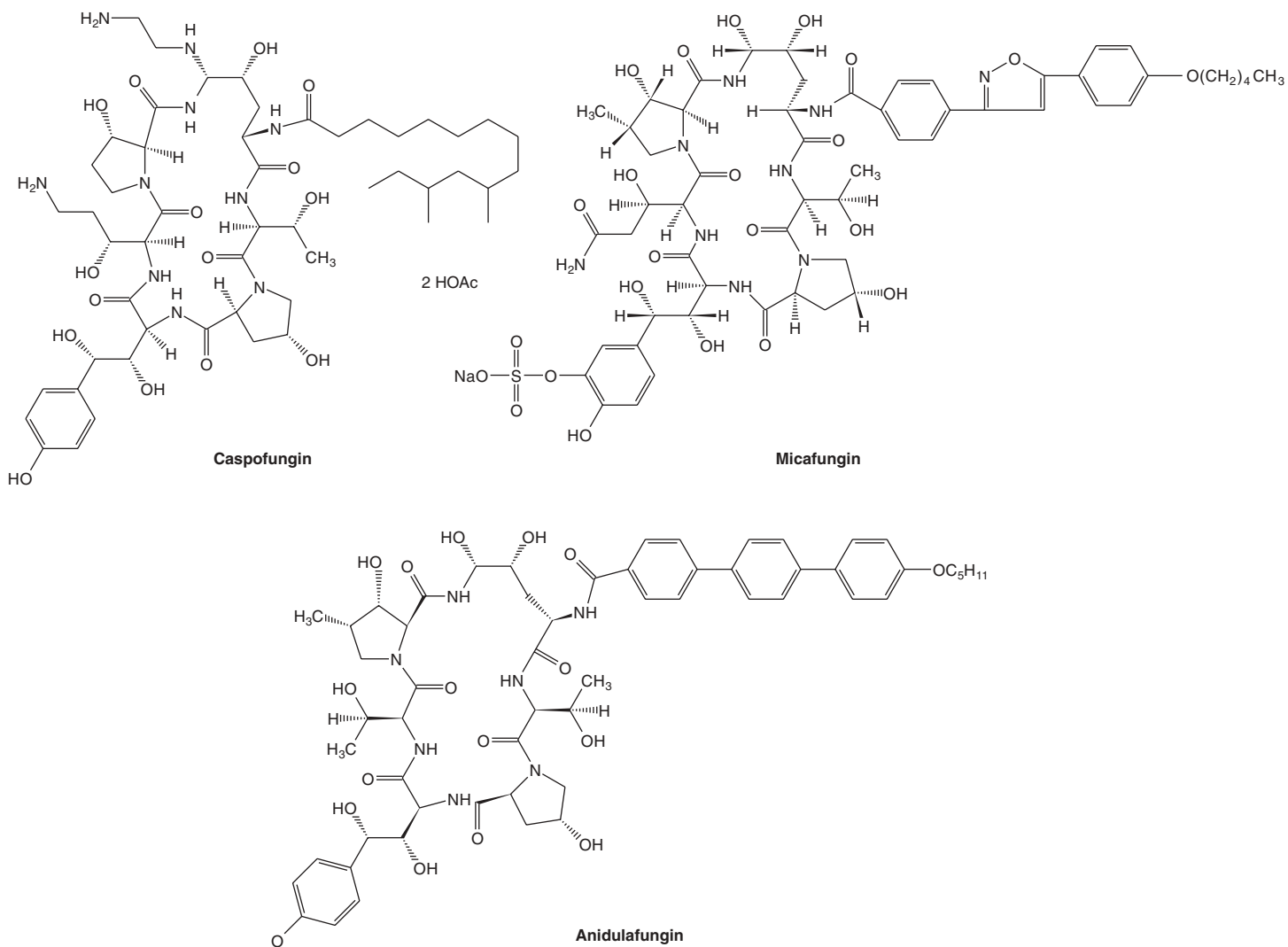**Caspofungin**

2 HOAc

Micafungin

Anidulafungin

Fig. 1. Chemical structures of caspofungin, micafungin and anidulafungin (reproduced from Boucher et al.,[16] with permission from Adis, a Wolters Kluwer business [© Adis Data Information BV 2004. All rights reserved.]).

1. Pharmacology

1.1 Chemistry

The echinocandins are large (molecular weight ~1200 kDa) semisynthetic lipopeptides chemically modified from natural products of fungi: caspofungin (Cancidas®, Merck and Co., Whitehouse Station, NJ, USA) from pneumocandin B of *Glarea lozoyensis*, anidulafungin (Eraxis®, Pfizer, New York, NY, USA) from echinocandin B_0 from *Aspergillus nidulans* and micafungin (Mycamine®, Astellas Pharmaceuticals, Deerfield, IL, USA) from the hexapeptide FR901370 from *Coleophoma empedri*.[11-13,19] Chemical structures of the three licensed echinocandins are shown in figure 1. The position and conformation of the N-linked acyl lipid side chains of these cyclic hexapeptides are critical to their antifungal activity.[25] Caspofungin has a fatty acid, micafungin a complex aromatic, and anidulafungin an alkoxytriphenyl side chain (figure 1). It is thought this side chain intercalates with the phospholipid bilayer of the fungal cell membrane. Caspofungin (acetate) is soluble in water and methanol, and micafungin (sodium) is soluble in water, whereas anidulafungin is soluble in neither water nor methanol.[11-13]

1.2 Mechanism of Action

The echinocandins are noncompetitive inhibitors of 1,3-β-D-glucan synthase (and, to a lesser extent, 1,6-β-D-glucan synthase), an enzyme complex within the fungal cell wall comprised of at least two subunits: Fks1p (encoded by the genes *FKS1, FKS2* and *FKS3*) and Rho1p. *FKS1* transcription is linked to cell wall remodelling in fungi and *FKS2* transcription is calcineurin dependent. Rho1p is a key regulatory protein, driving or arresting the synthesis of 1,3-β-D-glucan.[20] Specifically, the echinocandins target the *FKS1* gene product with Fks1p being the active site of the enzyme,[26,27] although the precise echinocandin-binding site remains unresolved. Fks1p inhibition is concentration dependent. Since 1,3-β-D-glucan is an integral component of the fungal cell wall, changes in its characteristics compromise osmotic stability resulting in cell lysis.[23,28] Human cells do not contain 1,3-β-D-glucan.[20]

The proportion of the fungal cell wall comprising glucan varies widely between fungal species and is typically predictive of echinocandin activity. For example, 1,3-β-D-glucan is more predominant in the cell walls of *Candida* and *Aspergillus* species (especially *C. albicans* and *Aspergillus fumigatus*), whilst zygomycetes lack this component. However, the cell wall of *Cryptococcus neoformans* contains 1,3-β-D-glucan yet the echinocandins demonstrate little activity against this pathogen (see section 2). This suggests that there are likely to be additional (or alternate) components of their mechanism of action.[29]

1.3 Formulations

Echinocandin preparations are for intravenous use only and it is unlikely that oral formulations will become available. Caspofungin is presented as a lyophilized white powder and excipients include sucrose, mannitol, acetic acid and sodium hydroxide. Once reconstituted, this formulation (pH 6.6) is incompatible with dextrose.[11,20] The drug is given by intravenous infusion over 1 hour and can be stored at 4°C for up to 24 hours post reconstitution. Micafungin is also prepared as a powder ready for reconstitution. Once reconstituted, the solution has a pH of 5–6, and is stable at room temperature for 48 hours if shielded from light. Micafungin can be infused with other solutions.[12] To reconstitute anidulafungin, the previous recommendation of reconstitution in 20% alcohol has been replaced by reconstitution in water for injection. Subsequently, the drug should be diluted with only 0.9% sodium chloride, or 5% glucose, for infusion.[13] With regard to the previous recommendation, although reconstitution in 20% alcohol may have been problematic for patients susceptible to disulfiram reactions (see section 5),[13] adults in phase I and II trials did not experience disulfiram-like reactions with coadministration of anidulafungin and metronidazole.[30] The recommended dosages in adults and children for caspofungin, micafungin and anidulafungin vary with indications and are discussed in section 7. In children, the recommended daily dose for caspofungin is 70 mg/m^2 followed by 50 mg/m^2 thereafter for all indications.[11,22]

2. Spectrum of Activity

2.1 *In Vitro* Minimum Inhibitory Concentration Breakpoints

As a drug class, the echinocandins not only demonstrate potent broad-spectrum *in vitro* activity against *Candida* and *Aspergillus* species but are also active against *Pneumocystis jirovecii*, although they have not been pursued for this last indication.[17,19,31] Comparison of minimum inhibitory concentrations (MICs) between studies must be interpreted in the context that data correlating *in vitro* susceptibility with *in vivo* outcomes are not robust and require validation in clinical trials. Results of MIC studies are further confounded by the use of multiple methodologies with different technical variables such as growth forms (yeast or mycelium forms) and method of endpoint determinations. The minimum effective concentration (MEC), or lowest drug concentration that results in the formation of blunt attenuated hyphal structures as viewed microscopically, has been proposed as a more meaningful morphological endpoint but is yet to be adopted as the standard in susceptibility testing.

Currently, there are two reference methods for broth microdilution antifungal susceptibility testing of echinocandins against *Candida* spp.: the Clinical and Laboratory Standards Institute (CLSI) method[32] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method.[33,34] Both use a 24-hour duration of incubation and a prominent inhibition (50% relative to growth control) MIC endpoint criterion,[33] but differ in the physical platform employed (round vs flat-bottomed microdilution wells), inoculum density, glucose content of medium and method of endpoint MIC reading (visual vs spectrophotometric). Head-to-head comparisons of the two methods involving caspofungin have yielded similar MICs with essential agreements (±2 dilutions) of 93–98%.[35,36]

Although EUCAST has not proposed clinical breakpoints (CBPs) for the echinocandins and *Candida*, the CLSI has established a consensus interpretative MIC CBP for susceptibility of ≤2 μg/mL for the three echinocandins and all species of *Candida*. Factors taken into account in establishing this breakpoint included (i) the fact that clinical resistance is rare (see section 2.4); (ii) mechanisms of resistance; (iii) the population distribution of MICs; (iv) parameters associated with success in pharmacodynamic models; and (v) results of clinical efficacy studies.[32,37-39] No CBP has been established for 'resistance'. However, it is noteworthy that MICs of *Candida* strains containing *FKS1* and/or *FKS2* mutations that are known to confer echinocandin resistance (see section 2.4) may not be above this CBP. Furthermore, kinetic studies of the glucan synthase complex indicate that a lower MIC cutoff (0.25–0.5 μg/mL) may be more sensitive for detection of strains with *FKS* mutations and that 'susceptibility' breakpoints of ≤2 ug/mL may be too high for anidulafungin and micafungin.[27,40] Studies defining the MIC distribution of wild-type *Candida* strains to establish epidemiological cutoff values (ECVs) for susceptibility for each echinocandin using the CLSI method showed that ECVs were 8- to 64-fold lower than the CBP for all species except *Candida parapsilosis* and *Candida guilliermondii*.[37] Most recently, Pfaller et al.[41] reported a high level of agreement between CLSI, EUCAST and E-test (AB Biodisk, Solna, Sweden) methods and of their ability to distinguish wild-type from *FKS* mutant strains of *Candida* using caspofungin, anidulafungin and micafungin; these results are consistent with those of another study.[33]

2.2 Comparison of Activity of Echinocandins

2.2.1 *Candida* spp.

All three echinocandins are fungicidal *in vitro* and *in vivo* against a broad range of *Candida* spp., including species that are intrinsically (or potentially) resistant to azoles (*C. krusei*, *C. glabrata*) or amphotericin B (*Candida lusitaniae*), and emerging species (e.g. *Candida famata*, *Candida rugosa*).[19,24] Comparative MIC data for caspofungin, micafungin and anidulafungin from two contemporary surveillance studies analysing >5346 global *Candida* isolates (collected in 2001–6) are summarized for the more common *Candida* species (as well as *Aspergillus* spp.)[42-45] in table I. In general, MIC required to inhibit growth of 90%

Table I. Echinocandin activity against common *Candida* and *Apergillus* species[23,24,42-45]

Organism	Caspofungin	Micafungin	Anidulafungin
***Candida* species**	**MIC$_{50}$, MIC$_{90}$**	**MIC$_{50}$, MIC$_{90}$**	**MIC$_{50}$, MIC$_{90}$ (range)**
C. albicans	0.03, 0.06	0.015, 0.03	0.03, 0.06 (0.03–0.25)
C. glabrata	0.03, 0.06	0.015, 0.015	0.06, 0.12 (0.03–1)
C. tropicalis	0.03, 0.06	0.03, 0.06	0.03, 0.06 (0.06–2)
C. krusei	0.12, 0.25	0.06, 0.12	0.06, 0.06 (0.12–1)
C. parapsilosis	0.25, 1	1, 2	2, 2 (0.12 to >2)
C. guilliermondii	0.5, 1	0.5, 1	1, 2 (1–4)
C. lustitaniae	0.25, 0.5	0.06, 0.12	0.5, 0.5 (0.125–2)
C. dubliniensis	–, 0.5	–, 0.03	–, 0.06
***Aspergillus* species**	**MEC$_{90}$[a] (range)**	**MEC$_{90}$[a] (range)**	**MEC$_{90}$[a] (range)**
A. fumigatus	0.12 (0.007–1)	0.03 (0.007–0.25)	0.03 (0.007–0.12)
A. flavus	0.06 (0.007–1)	0.015 (0007–1)	0.015 (0.007–0.25)
A. terreus	0.03 (0.007–2)	0.015 (0.007–0.25)	0.015 (0.007–0.5)

a MEC$_{90}$ values and MEC$_{90}$ range values were from Pfaller et al.[45] and Antachopoulos et al.[44]

MEC = minimum effective concentration; **MIC$_{50}$** = minimum inhibitory concentration at which the growth of 50% of the isolates tested were inhibited; **MIC$_{90}$** = minimum inhibitory concentration at which 90% of isolates tested were inhibited; – indicates not available.

of organisms (MIC$_{90}$) values for the echinocandins are ≤2 μg/mL. Consistent with earlier studies, 100-fold higher MIC required to inhibit growth of 50% of organisms (MIC$_{50}$) and MIC$_{90}$ results were noted for *C. parapsilosis* and *C. guilliermondi*;[23,42,43,46] caspofungin and anidulafungin (but not micafungin) MICs for *C. lusitaniae* were also higher than those for, for example, *C. albicans*. The relatively higher MICs (although still within the 'susceptible' MIC range for caspofungin[32]) for *C. parapsilosis* are a particular concern since this species is the second or third most common cause of candidaemia and is a prominent fungal pathogen in paediatric patients.[4,47,48]

In general, *in vitro* activity against *Candida* spp. is comparable amongst the three echinocandins (table I). Furthermore, when compared in the presence of serum (human serum decreases the potency of all echinocandins), MIC differences are minimized, suggesting that *in vivo* activity will be similar between echinocandins.[49,50] Nonetheless, minor variations in MICs have been observed between the three drugs.[23,42,43] In one review,[51] anidulafungin was found to display the lowest MIC values against *Candida*, followed by micafungin and caspofungin. In another study, the inhibitory activity of micafungin was 5- to

10-fold greater than that of caspofungin against *C. albicans*, *C. glabrata*, *Candida tropicalis* and *Candida dubliniensis*.[52] Minor differences in minimum fungicidal concentrations (MFCs) between agents have also been noted.[26] MFCs of micafungin against *C. glabrata* range from 0.01 to 0.3 μg/mL compared with 0.12–2 μg/mL for anidulafungin and 0.5–8 μg/mL for capsofungin. MFCs of echinocandins against *C. parapsilosis* and *C. guilliermondii* are 4–8 μg/mL.[53]

There are limited data suggesting that anidulafungin displays low MICs against strains of *C. parapsilosis* with elevated MICs to caspofungin and micafungin. Scanning electron microscopy has revealed that non-caspofungin-susceptible strains of *C. parapsilosis* undergo morphological distortion at comparatively lower concentrations of anidulafungin (1 μg/mL) than caspofungin (16 μg/mL),[54] although this phenotype of *C. parapsilosis* has not been observed to occur outside of this report. However, the apparent greater potency of anidulafungin against such 'caspofungin-resistant' *Candida* isolates is likely to be of doubtful clinical significance. *C. glabrata* isolates with caspofungin MICs of 8–64 μg/mL have also been reported to display low MICs to anidulafungin (2–4 μg/mL).[55] Of interest, *Candida orthopsilosis* and *Candida metapsilosis* isolates have

been reported to have significantly lower echino-candin MICs than *C. parapsilosis*.[56]

In experimental models of infection, all three echinocandins have reduced fungal colony counts and improved survival against a range of *Candida* species, although earlier studies suggested that caspofungin was less effective in reducing fungal burden in neutropenic mice with *C. glabrata* and *C. krusei* infection.[20,23,24] In mice with *C. krusei* infection, administration of anidulafungin improved survival and reduced organism burden when compared with placebo, fluconazole and amphotericin B.[57] However, studies correlating *in vitro* MIC results with outcome have produced conflicting results. In one study, patients with *Candida* isolates of MICs of >2 μg/mL had superior outcomes compared with those displaying MICs of <1 μg/mL;[58] however, only a small number (n = 3) of isolates displayed MICs of >2 μg/mL. In a mouse kidney infection model, *C. parapsilosis* strains with the highest MICs responded *in vivo* to the lowest dose of antifungal drugs, whilst isolates with the lowest MICs required the highest dose for a similar response.[59]

Aspergillus spp.

Although fungistatic against *Aspergillus* spp., the echinocandins exhibit excellent *in vitro* and *in vivo* activity against many species – *A. fumigatus*, *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* (table I) – at lower concentrations than amphotericin B and itraconazole, where they result in injury to the hyphal tips.[44,45,60,61] Unlike with *Candida* spp., MICs are difficult to determine and the MEC may be a better measure of susceptibility of *Aspergillus*. 1,3-β-D-glucan is incorporated at the apical growing tips of *Aspergillus* hyphae and is the location where echinocandins exert their effect,[62] leading to characteristic swollen, stubby hyphae and clumping when visualized on microscopy; the MEC is the lowest drug concentration resulting in these changes.[18,51,60] The vast majority (>99%) of isolates have been inhibited by ≤0.06 μg/mL of all three drugs.[45] Antachopoulos et al.[44] compared MECs and inhibition of metabolic activity for the echinocandins using germinated and nongerminated *Aspregillus* conidia; anidulafungin exhibited the lowest MECs and caspofungin the highest for non-germinated conidia. However, with germinated conidia, for each drug and each species tested, metabolic inhibition measures did not differ significantly. Another study[45] of 526 isolates confirmed that the inhibitory activities of all three agents were comparable, although MECs of micafungin and anidulafungin were 2- to 10-fold lower than for caspofungin (table I).

As single agents, the echinocandins are effective in reducing fungal burden and/or prolonging survival in animals with disseminated aspergillosis.[23,63,64] There are also data indicating synergistic or additive effects against *Aspergillus* spp. of combination therapy of an echinocandin with a polyene or azole. Micafungin and itraconazole were synergistic *in vitro* against ~50% strains of various *Aspergillus* spp.[65] Studies in rabbits suggest synergism between anidulafungin and voriconazole in invasive pulmonary aspergillosis (IPA).[66] Addition of amphotericin B to the combination of voriconazole and caspofungin further enhanced synergy against *A. terreus*.[67]

Other Fungi

The echinocandins have little useful activity against the Zygomycetes, *Fusarium* spp., *Scedosporium polificans*, *Cryptococcus* spp. and *Trichosporon* spp.,[20,26] and have variable activity against dematiaceous fungi and *Penicillium* spp.[26,68] Although they are active against the mycelial forms of dimorphic fungi, MICs are high for the yeast forms and this precludes their use for the treatment of infections caused by these fungi.[23,28,60] Synergy between caspofungin and amphotericin B lipid complex has been demonstrated in mouse models of disseminated *Rhizopus oryzae* infection where combined use of both agents resulted in significantly improved survival compared with either therapy alone;[19] *in vitro* synergy was also seen when caspofungin was combined with terbinafine for *Fusarium* spp.[69] *In vitro* susceptibility data for synergy are sparse for the other two echinocandins.

2.3 Activity Against *Candida*-Generated Biofilms

A novel aspect of the antifungal activity of the echinocandins is their effect on *Candida*-generated

biofilms within which sessile *Candida* cells become embedded. Biofilms are often refractory to treatment with antifungal drugs, presumably due to altered efflux pump mechanisms and diminished sterol synthesis.[70,71] *In vitro* models of biofilm infection[72] have shown that both caspofungin and micafungin are effective in killing (≥99%) preformed *C. albicans*- and *C. parapsilosis*-related biofilms at concentrations achievable *in vivo* and at a magnitude similar to that for amphotericin B. Choi et al.[73] reported that the caspofungin MIC required to inhibit growth of 80% of organisms for sessile cells of *C. albicans* and *C. glabrata* were 0.5 and 1 μg/mL, respectively (corresponding micafungin results, 0.5 and 0.25 μg/mL), but neither drug was effective against *C. tropicalis* and *C. parapsilosis*. Caspofungin also prevents adherence of *C. albicans* to epithelial cells, thereby inhibiting the early phase of biofilm development,[74] but when used in combination with amphotericin B or fluconazole, no synergistic effects were seen. Whether *in vitro* models of biofilm infection are applicable in the clinical setting merits further investigation. Animal studies indicate that the use of caspofungin line locks reduces the incidence of disseminated disease in mice with central venous catheters infected with *Candida* biofilms; anidulafungin also appears effective against biofilms.[75,76]

2.4 Echinocandin Resistance

Despite the occurrence of spontaneous resistance to echinocandins of *Candida* spp. *in vitro*, clinical resistance remains rare. Contemporary surveillance studies of large numbers of clinical isolates have revealed no evidence of emerging caspofungin, or other echinocandin, resistance.[42,43,46,77,78] Nonetheless, elevated MIC values with occasional treatment failures have been reported for strains of *Candida* (see section 2.4.1). Clinical failure has been restricted to case reports of resistance to caspofungin where serial isolates from the same patient receiving extended courses of therapy have demonstrated step-like increases in MIC, or in small numbers of patients with breakthrough infection whilst receiving echinocandin therapy. Clinical resistance has been de-

scribed for *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei* and *C. dubliniensis*,[79-84] yet an uncertain correlation exists between clinical failure and elevated MICs.

2.4.1 Fks1p Amino Acid Substitutions in *Candida*

Echinocandin resistance in *Candida* spp. has been attributed to mutations in the *FKS1* gene subunit (to a lesser extent in *FKS2*) resulting in amino acid substitutions in conserved regions of Fks1p.[85-88] The mechanistic evidence for altered echinocandin sensitivity has been recently discussed by Perlin[80] but is not well understood. Earlier genetic studies using *Saccharomyces cerevisiae* as a model pathogen identified two 'hot spot' regions within Fks1 that conferred reduced susceptibility to caspofungin – 'hot spot' 1 (HS1) and 'hot spot' 2 (HS2).[80] Resistance mutations in HS1 fall within an 89 amino acid domain that is predicted to lie on the cytoplasmic aspect of the plasma membrane. It is unclear whether this region comprises part of the binding domain for echinocandin drugs or affects drug action indirectly. The most compelling evidence for Fks1 modification as the principal mechanism of resistance is the observation that these 'hot spot' mutations significantly decrease the drug sensitivity of glucan synthase, with all *FKS* mutants having altered glucan synthase enzyme kinetics.[80] *FKS1* mutations have also been identified in micafungin-resistant laboratory *C. albicans* strains following exposure to micafungin.[85]

Clinical *C. albicans* isolates with high MIC values for caspofungin, including those from patients who have failed therapy with the drug, have shown a wide range of amino acid substitutions within HS1 of Fks1p. These strains remain uncommon.[80,81] Most substitutions have been found at position 645 (serine) – in particular, S645F (serine to phenylalanine), S645P (serine to proline) and S645Y (serine to tyrosine) mutations.[88] Although strains containing these mutations generally have reduced echinocandin susceptibility in animal models, not all *FKS1* mutant *C. albicans* strains have caspofungin MICs of ≥2 μg/mL.[80,88]

In *C. krusei*, HS1 mutations, as well as an additional mutation in HS2 (Arg1352Ser) that

conferred resistance, have also been identified.[88] Furthermore, amino acid polymorphisms within the Fks1 HS1/HS2 regions appear to account for intrinsic reduced susceptibility of *C. parapsilosis* and *C. guilliermondii* to echinocandins.[80] In *C. parapsilosis*, a gene polymorphism that results in substitution of alanine for proline at Pro649 may be of particular relevance. *C. orthopsilosis* and *C. metapsilosis* strains may also harbour the P649A polymorphism and may also contain the I1359V polymorphism within HS2 that results in reduced susceptibility.[86,88]

An intriguing question is whether resistance to one echinocandin confers cross-resistance to others or to the entire class. Amongst *Candida* spp., it appears that cross-resistance generally occurs since the presence of *FKS1* mutations results in resistance; however, the fold-change relative to the susceptible wild-type strain appears to be greater for micafungin (MICs 1–16 µg/mL) and caspofungin (MICs 4 to >16 µg/mL) than for anidulafungin (MICs 0.5–2 µg/mL).[80] Pfeiffer et al.[87] sequenced the 'hot spot' regions of the *FKS* gene of 17 *Candida* isolates recovered from 12 patients with breakthrough IC whilst receiving micafungin. 'Hot spot' mutations were found in five *C. glabrata* and two *C. tropicalis* isolates; of these, five (all *C. glabrata*) demonstrated micafungin MICs of >2 µg/mL but all seven had caspofungin MICs of >2 µg/mL. Five *C. parapsilosis* isolates (micafungin MIC >2 µg/mL) had wild-type *FKS* sequences and were susceptible to caspofungin (MICs 0.5–1 µg/mL). It is possible, although not proven, that the naturally occurring polymorphism within the *C. parapsilosis FKS1* gene (see previous paragraph) may also be responsible for elevated micafungin MICs (>2 µg/mL) and clinical breakthrough.[87]

Notably, when tested for susceptibility in the presence of serum, the MIC of all *FKS1* mutant strains was ≥2 µg/mL for all three echinocandins.[40] The clinical significance of this observation is not yet known. The possibility that anidulafungin may have superior activity against *C. parapsilosis* has also been raised (see section 3). In one study, a number of caspofungin- and micafungin-resistant *C. parapsilosis* isolates (MIC 64 µg/mL) from patients in a burn unit exhibited

MICs of 1–2 µg/mL to anidulafungin.[54] In another report, resistance occurred to caspofungin and micafungin but not to anidulafungin.[83] Broad resistance extending to amphotericin B and the azoles has occurred but is rare.

Reduced susceptibility in *Candida* spp. has been associated with increased chitin production, and overexpression of the *RER1* (regulator of echinocandin resistance) and the *CDR2* efflux pump genes.[80,89,90] Paderu et al.[91] have shown that a high-affinity facilitated diffusion transporter mediates caspofungin entry into *C. albicans*; disruption of this system represents a potential mechanism of resistance.

2.4.2 *Aspergillus* spp. and Non-*Candida* Yeasts

Resistance mechanisms have been elucidated for *A. fumigatus*. At least one strain with a target-site mutation conferring low-level resistance has been identified whilst another, considered resistant, demonstrated a 'paradoxical' effect (see section 2.5).[92] Resistant *Aspergillus* species have been observed only in the laboratory.[80]

The 1,3-β-D-glucan synthase enzyme in *C. neoformans* is sensitive to the echinocandins yet these agents have no useful *in vitro* or *in vivo* activity against this fungus. The mechanism of resistance in non-*Aspergillus* moulds with high (>16 µg/mL) MICs is also unknown but is likely not due to target insensitivity. Glucan synthase activity from a number of moulds has been shown to be strongly inhibited by caspofungin *in vitro*.[29,68] It has been suggested that melanization reduces the susceptibilities of *C. neoformans* and *Histoplasma* spp. to caspofungin.[93]

2.5 'Paradoxical Effect' or Drug Resistance?

The 'paradoxical' or 'Eagle-like' effect refers to significantly increased growth *in vitro* of echinocandin-susceptible organisms at supra-MICs.[94] However, increasing the concentration even further results in cessation of growth. This phenomenon has been observed in *Candida* and *Aspergillus* spp. *in vitro*; it appears to be species-related and varies with the echinocandin. The effect has been noted most often for caspofungin, and is not related to *FKS1* mutations or upregulation of echinocandin

sensitivity of the glucan synthase complex in the presence of drug.[95] Early studies suggested that when *C. albicans* is exposed to high caspofungin concentrations, genes encoding chitin are rapidly but transiently induced to compensate for decreased synthesis of β-1,3-glucan.[96] It has also been postulated that stress response pathways such as the cell wall integrity and calcineurin pathways play a critical role.[96-98] Chamilos et al.[98] noted species differences in paradoxical growth at high caspofungin concentrations (prevalence 90%, 60%, 40% and 10% in *C. parapsilosis*, *C. albicans*, *C. tropicalis* and *C. krusei*, respectively). For micafungin, the paradoxical effect was observed in *C. tropicalis* (prevalence 70%) and *C. krusei* (60%), whilst for anidulafungin, the effect was seen only in *C. albicans* (prevalence 40%) and *C. tropicalis* (20%). No strains of *C. glabrata* exhibited paradoxical growth with any of the three drugs.[98]

Results of *in vivo* animal studies are contradictory. Some studies demonstrated the same 'Eagle-like' effect in rabbits and mice with IPA accompanied by a paradoxical increase in other markers of invasive disease and fungal burden,[94,99,100] yet other mouse models have not.[101] Addition of mouse serum eliminated the paradoxical effect. The clinical relevance of this *in vitro* effect is uncertain. Supra-therapeutic blood concentrations have been observed in pharmacokinetic studies in healthy volunteers and can be expected to occur in patients if larger doses of echinocandins are used in the future.

3. Pharmacokinetics

3.1 General Properties

As a class, the echinocandins have low oral bioavailability (<0.2% for caspofungin) and high protein binding (>99%) [table II].[11-13,19,102] They distribute well into tissues including lung, liver and spleen, but with minimal penetration into the CNS and eye due to their high protein binding and large molecular weights.[20,23,24] Consequently, they are not recommended for meningeal or eye infections; failure of caspofungin in treatment of *Candida* endophthalmitis has been reported (see section 7). Urinary concentrations of parent drug

are low (table II), yet one study documented a favourable response to caspofungin in 11 of 12 patients with fungal urinary tract infection.[103] Echinocandins are not dialyzable and do not require dose adjustment in renal insufficiency.

All three agents exhibit linear pharmacokinetics after intravenous administration. Following initial distribution, echinocandins are taken up by red blood cells (shown for micafungin) and degraded slowly, primarily in the liver (but also in the adrenal glands and spleen) by hydrolysis and *N*-acetylation (shown for caspofungin and micafungin) to inactive metabolites.[11-13,20] However, two minor micafungin metabolites exhibit antifungal activity. Degradation products are excreted over many days primarily via bile. Biliary caspofungin concentrations are reportedly ~30% that of serum.[11] All echinocandins are poor substrates for, or do not inhibit, cytochrome P450 (CYP) enzymes; neither are they substrates for the intestinal or tissue P-glycoprotein transport systems.[17] *In vitro*, caspofungin is taken up via the OATP-1B1 transporter, which also transports drugs such as rifampicin (rifampin) and ciclosporin.[104] Although not known, it is unlikely that micafungin and anidulafungin also utilize this pathway since they interact less with ciclosporin[23,105] (see section 5).

There are interesting pharmacokinetic disparities between the three agents. Anidulafungin is unique in being eliminated almost exclusively by slow chemical degradation in bile rather than via hepatic metabolism; compared with caspofungin and micafungin, it has a lower maximum concentration (C_{max}) but much longer half-life, and larger volume of distribution and faster clearance (table II).[13,19,20] Tissue concentrations are ~10-fold that of plasma.[13] Steady-state concentrations of anidulafungin are achieved after a loading dose and one subsequent dose after 4 days of treatment for micafungin, whilst for caspofungin they are not achieved for more than 2 weeks after starting therapy.[11-13] The steady-state area under the concentration-time curve (AUC) of anidulafungin is much less than those of the other two agents at nearly equivalent doses.[20] High protein binding (table II) could limit the amount of drug available for activity, yet other antifungal drugs that are highly protein

Table II. Comparison of major properties and key pharmacokinetic parameters of echinocandins in adults[a][17,20,51]

Variable	Caspofungin	Micafungin	Anidulafungin
C_{max} (mg/L) [50 mg single dose]	7.64	4.95	2.07–3.5
Bioavailability (%)	<10	<10	2–7
$t_{1/2}$ (h)	9–11	11–17	24–26
Vd (L/kg)	0.14	0.22–0.24	0.5
AUC (mg • h/L)	87.9–114.8	111.3	44.4–53
Protein binding (%)	96–97	99.8	>99
Metabolism	Slow peptide hydrolysis, N-acetylation and spontaneous degradation to inactive product	Catechol-*O*-methyltransferase pathway	Not metabolized Slow chemical degradation to inactive metabolites
Cl_T	0.15	0.185	0.26
Fraction excreted unchanged in urine (%)	1.4	0.7	<1
Elimination	35% faeces, 41% urine, 1.4% as unchanged drug	40% faeces, <15% urine	Primarily faeces (<10% as intact drug), 1% urine
CSF penetration (% plasma)	Low	Low	<0.1%
Dose adjustment in renal insufficiency	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
Dose adjustment in geriatric patients	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
Dose 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	Child-Pugh 7–9: C_{max} not altered, AUC significantly decreased compared with healthy subjects	No dose adjustment needed in patients with mild, moderate or severe hepatic dysfunction

a   Data are from multiple sources and are not always comparable.

AUC = area under the plasma concentration-time curve; **Cl$_T$** = total clearance; **C$_{max}$** = maximum concentration; **CSF** = cerebrospinal fluid; **t$_{1/2}$** = elimination half-life; **Vd** = volume of distribution.

bound such as amphotericin B and itraconazole are effective in treating fungal infections.

The relationship between echinocandin blood (or tissue) concentrations and treatment outcomes is currently undefined. High-performance liquid chromatography, with or without mass spectrometry methods, have been used to quantify echinocandins in blood and other clinical specimens such as bronchoalveolar lavage fluid.[106,107] However, clinical studies are required to determine if therapeutic drug monitoring may increase the efficacy of these agents.

3.2 Maximum Tolerated Dose

Maximum tolerated doses have not been established for anidulafungin and micafungin. Doses as high as 8 mg/kg of micafungin and 130 mg of anidulafungin daily have been administered to small numbers of patients without ill effects.[20] In

monkeys, hepatic necrosis occurred at doses of 5 and 8 mg/kg/day of caspofungin but not with 2 mg/kg/day.[11] Detailed pharmacokinetic studies in overweight/obese patients are needed to determine optimal dosing. One study[108] in surgical intensive care unit (ICU) patients showed that trough caspofungin concentrations were significantly higher in patients weighing <75 kg. A population pharmacokinetic analysis of micafungin also found increased serum clearance of drug in patients weighing ≥66.3 kg,[109] with a daily dose of 150 mg necessary to achieve the same 24-hour AUC as that attained by 100 mg daily doses in lower-weight patients.

3.3 Pharmacokinetics in Special Populations

3.3.1 Hepatic Insufficiency

The AUC of caspofungin is significantly increased in patients with moderate (Child-Pugh 7–9) hepatic

insufficiency (table II);[11] in contrast, that of micafungin is decreased.[12,110] This is likely due to an increased volume of distribution and lower protein binding in these populations. Anidulafungin concentrations are not increased in subjects with mild (Child-Pugh 5–6), moderate or severe (Child-Pugh >9) hepatic insufficiency.[13] It is recommended that the maintenance dose of caspofungin (but not micafungin or anidulafungin) be decreased from 50 to 35 mg daily in patients with moderate liver failure. Due to the limited clinical experience in patients with severe liver failure at the time of writing, there are no recommendations for dose adjustments of caspofungin and micafungin.

3.3.2 Paediatrics

The pharmacokinetics of echinocandins in children share many similarities with those in adults (table II). There has been much interest with regard to dosing of the echinocandins in children. In a cohort of 39 neutropenic children up to 17 years of age,[111] weight-based dosing of caspofungin resulted in significantly lower plasma concentrations than those achieved in adults receiving typical doses. However, dosing based on body surface area (50 mg/m^2/day) resulted in steady-state AUCs similar to those in adults receiving 50 mg/day, with similar results in older infants and toddlers.[112] Recently, serum concentrations from 12 neonates 1–11 weeks of age were evaluated on days 1 and 4 after doses of 25 mg/m^2/day; reduced daily doses of 25 mg/m^2/day were needed in infants <3 months of age.[113] Pharmacokinetics for micafungin in 9- to 17-year-old patients with febrile neutropenia are similar to those in adults. In a multicentre phase I sequential group dose-escalation (0.5–4 mg/kg) study, a 1.3- to 1.5-fold increase in clearance of micafungin was noted in patients 2–8 years of age compared with older children; hence, a dosage of 1.4 times that of the adult dose may be required in children younger than 8 years old.[113] Another study showed that in premature infants (mean gestational age 26.4 weeks) micafungin had a shorter half-life and more rapid plasma clearance than in older children and adults, suggesting that higher milligram/kilogram doses are needed.[114] Hope and colleagues[115,116] developed a micafungin dosing model in paediatric patients from population-based data, providing more support that patients of lower weight require higher milligram/kilogram doses to achieve desired drug concentrations[115] and that doses of 0.75–15 mg/kg can be used with safety.[116] Importantly, a dosage of micafungin 10 mg/kg achieved near maximal rates of decline in fungal burden within the CNS of infants with haematogenous Candida meningoencephalitis.[116] Additional studies are needed to establish dosing recommendations across the paediatric age continuum.

In the only study of anidulafungin, its administration in 24 neutropenic children aged 2–17 years showed that concentrations and exposures following maintenance doses of 0.75 and 1.5 mg/kg/day were similar to those observed in adults following maintenance doses of 50 and 100 mg/day, respectively.[13,117]

3.3.3 Pregnancy and Lactation

The echinocandins are categorized as Pregnancy Category C.[11-13] Anidulafungin and caspofungin cross the placenta in rats and have been detected in fetal plasma, but there are no systematic pharmacokinetic studies in pregnant women. The agents are found in the milk of lactating rats receiving the drug but it is not known whether they are excreted in human milk. The echinocandins should be used in pregnant and lactating women only if the clinical benefit justifies the risk.

Dosage adjustments are not required on the basis of race and sex as drug pharmacokinetics are similar among Caucasians, Hispanics, Blacks and Asians.[11-13] Elderly patients metabolize caspofungin slightly more slowly than younger adults but dose adjustment of drug is not required (table II).[20]

4. Pharmacodynamics

Despite excellent in vitro activity against Candida and Aspergillus spp., and favourable pharmacokinetics, treatment outcomes in patients with IFIs treated with echinocandins remain less than optimal.[14,15,21] As such, the need to optimize antifungal dosing and administration by exploiting

Table III. Pharmacodynamic parameters for echinocandins

Echinocandin	Outcome/endpoint predictor[a]		References
	in vitro	*in vivo* animal	
Caspofungin			
Candida spp.	Concentration-dependent, fungicidal	AUC/MIC	55,119,120
Aspergillus spp.	Concentration-dependent, fungistatic	C_{max}/MEC range 10–20	100,121
Micafungin			
Candida spp.	Concentration-dependent, fungicidal	AUC/MIC near 20	98,122-125
Aspergillus spp.	Concentration-dependent, fungistatic	C_{max}/MEC	44,126-128
Anidulafungin			
Candida spp.	Concentration-dependent, fungicidal	C_{max}/MIC, AUC/MIC	124,129,130
Aspergillus spp.	No data at time of writing	None noted	130,131

a The outcome/endpoint predictor for caspofungin, anidulafungin and micafungin in clinical studies of candidiasis and aspergillosis remain unknown at the time of writing.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum concentration; **MEC** = minimum effective concentration; **MIC** = minimum inhibitory concentration.

their pharmacodynamic properties is imperative. The pertinent aspects of echinocandin pharmacodynamics are detailed in a recent review.[118] Both *in vitro* and animal models have been useful in elucidating the pharmacodynamic parameters of echinocandins (table III).

For *Candida* spp., all three drugs display concentration-dependent fungicidal killing over a broad concentration range *in vivo* (table III), with efficacy that is best correlated with C_{max}/MIC or AUC/MIC ratios, as demonstrated in mice with systemic candidiasis.[55,60,119,127,132] Using standard drug doses, serum concentrations of >1 μg/mL are typically attained,[133] leading to consensus for the CLSI CBP of ≤2 μg/mL[32] to designate an isolate as 'susceptible'. The echinocandins also exhibit prolonged postantifungal effects (PAFE) against *Candida* spp.[55,119,127,129] The PAFE for caspofungin against *C. albicans* was noted to be >12 hours when concentrations exceeded the MIC.[130] The PAFE for micafungin against *Candida* spp. ranged from 0.9 to >20.1 hours depending upon the concentration tested;[120] concentrations 4 times the MIC produced the longest PAFE. For anidulafungin, PAFEs of >12 hours have also been observed.[127] Given the PAFE, extended dosing intervals (currently once daily) could be an option.[118] Caspofungin concentrations in tissues remain high even after serum concentrations have declined and antifungal ef-

ficacy persists after serum concentrations fall below the MIC.[132] In one study, equivalent killing was observed in *Candida* isolates exposed to caspofungin for only 1 hour (followed by drug washout) compared with those exposed for 24 hours.[131] Anidulafungin also achieves high tissue concentrations.[13]

There are relatively few data on the pharmacodynamics of echinocandins and *Aspergillus* spp. The efficacy of their fungistatic concentration-dependent activity is best correlated with C_{max}/MEC ratios.[100,118,133] A much shorter PAFE (≤0.5 hours) for both caspofungin and micafungin relative to that seen with caspofungin against *Candida* spp. is observed with *A. fumigatus*.[134] In a recent Monte-Carlo simulation study, different doses of micafungin were evaluated in 48 plasma samples (ten patients) to determine the optimal effective concentration against *Aspergillus* spp., in this case >0.05 μg/mL. To reach this target, micafungin doses of at least 100 mg twice daily or 250 mg once daily were required to achieve a favourable outcome.[135] However, plasma concentrations may not be the best marker of drug activity since they may not correlate with concentrations at the site of infection, which are especially important in IA. A recent study evaluated micafungin concentrations in plasma as well as in the alveolar macrophages and epithelial lining fluid. Markedly higher concentrations were mea-

sured in plasma than in epithelial lining fluid and alveolar macrophages. However, at 24 hours, the concentrations in alveolar macrophages were higher than plasma or ELF.[107]

Published *in vivo* studies of pharmacodynamic properties of echinocandins against *Aspergillus* spp. are also relatively sparse but suggest that the 'paradoxical effect' occurs (see section 2.5). Two murine models of IPA have documented concentration-dependent activity in neutropenic mice administered caspofungin[100] and correlation of the C_{max}/MEC with reduction in fungal burden in the lungs. In one study, an increase in fungal growth was noted as caspofungin concentrations increased.[124] Studies in neutropenic mice and rabbits treated with micafungin have similarly demonstrated a dose-dependent response in survival but have shown conflicting results regarding fungal burden and dosage escalation.[123-125,128] Dose-dependent hyphal injury was noted with most damage occurring in the 20 mg/kg/day group, consistent with previous observations.[136]

The pharmacodynamic properties of the echinocandins against pathogens other than *Candida* and *Aspergillus* spp. are uncertain. Limited data are available regarding dose escalation of the drugs in *R. oryzae* and *Fusarium* infections.[118] Caspofungin has been shown to reduce *R. oryzae*

burden in the brain and improve survival in mice at low, but not at high, doses.[137]

5. Drug Interactions

There are few serious drug-drug interactions with the echinocandins as a result of their unique antifungal mechanism of action and the fact that they are not appreciable substrates, inhibitors or inducers of the CYP or P-glycoprotein systems. Overall, caspofungin appears to have the most, whilst anidulafungin has the least, drug interactions. Micafungin is a substrate and a weak inhibitor of CYP3A *in vitro*; however, hydroxylation by CYP3A is not a major pathway for its metabolism *in vivo*.[12,60] The more important known interactions are shown in table IV.

Slight increases in caspofungin clearance have been seen when combined with powerful inducers or inhibitors of hepatic metabolism, notably rifampicin, but also phenytoin, efavirenz, carbamazepine and dexamethasone. The manufacturer recommends increasing the dose of caspofungin to 70 mg/day in adult patients and 70 mg/m^2 (but not exceeding 70 mg daily) in children with concomitant use of rifampicin and to consider a similar dose increase when used with phenytoin, efavirenz, carbamazepine or dexamethasone.[11,138] The interaction of caspofungin with rifampicin

Table IV. Drug interactions with the echinocandins[11-13,138-142]

Drug	Caspofungin	Micafungin	Anidulafungin
CYP/P-glycoprotein interactions	Poor substrate for CYP Not an inhibitor of CYP Not a substrate/inhibitor of P-glycoprotein	Substrate for CYP3A4 Weak inhibitor CYP3A4 Not a substrate/inhibitor of P-glycoprotein	Not a substrate, inducer or inhibitor of CYP
Tacrolimus	AUC, peak and 12-hour concentrations of tacrolimus are decreased by ~20%	No significant effect on tacrolimus	No significant effect on tacrolimus
Sirolimus	No data	Increases AUC of sirolimus by 12%	No data
Ciclosporin	35% increase in the AUC of caspofungin	Decreases clearance of ciclosporin by 16%	22% increase in AUC of anidulafungin; dose adjustment not required
Rifampicin	Decreases steady-state plasma caspofungin concentrations	No significant effect on micafungin	No significant effect on anidulafungin
Voriconazole	No data	No significant effect on micafungin	No significant effect on anidulafungin
Nefidipine	No data	Increases the AUC and C_{max} of nifedipine by 18% and 43%, respectively	No data

AUC = area under the plasma concentration-time curve; **C$_{max}$** = maximum concentration; **CYP** = cytochrome P450.

results in additional exposure to both compounds since rifampicin is an inhibitor, and ultimately also an inducer (following multiple doses), of OATP-1B1.[20,138] During the first day of rifampicin coadministration, a transient 61% increase in the AUC of caspofungin occurs; however, after 14 days, a 14–31% reduction in trough caspofungin concentrations is observed.[19] Concurrent use of rifampicin or other substrate/inhibitors of CYP, including voriconazole with anidulafungin or micafungin, does not affect serum concentrations of these agents.[12,13,23,24]

There are modest interactions with the calcineurin inhibitors (table IV) – raised plasma caspofungin concentrations result (35% increase in AUC) in association with elevated transaminase levels[11] but not with significant adverse effects. Since both ciclosporin and caspofungin are substrates of the OATP-1B1 transporter,[104] it offers a plausible although unproven explanation for their interaction with caspofungin. Coadministration of ciclosporin and anidulafungin has revealed a 22%, albeit not clinically significant, increase in the AUC of anidulafungin after 4 days of concomitant therapy.[140] Micafungin decreases clearance of ciclosporin by 16%; in one study, 5 of 28 (18%) subjects experienced a significant change (>25%) in clearance, and hence monitoring of ciclosporin concentrations is recommended.[141] Caspofungin reduces the AUC (by ~20%), peak concentrations and 12-hour concentrations of tacrolimus, necessitating close monitoring of blood tacrolimus concentrations in those receiving concomitant caspofungin and tacrolimus therapy.[11] Anidulafungin and micafungin do not significantly affect the AUC of tacrolimus in volunteers (table IV).[20,139,142]

Patients at risk for disulfiram reactions who received anidulafungin under the previous recommendations of dissolution of drug in 20% alcohol, should be monitored carefully.[13,30] This is no longer a concern with the current recommendation of reconstituting the drug in water. Micafungin may increase the blood concentrations of drugs metabolized by the CYP3A4 system, including sirolimus and nifedipine (by 18%), entailing the need for monitoring for increased nifedipine effects and possible dose adjustment of these drugs.[12]

6. Safety Profile

Echinocandins are contraindicated for use in patients with known hypersensitivity to this drug class. All agents include a warning of possible hepatic dysfunction including hepatic failure,[11-13] yet they are very safe when compared with other classes of antifungals. All three drugs are safe to use in children as well in adults.[111,113,114] The few adverse events that have been noted generally have not been serious. More events, including infusion reactions and hepatotoxicity, have been noted for caspofungin, but this is likely to be related to the longer time that this agent has been in use.[17]

Thrombophlebitis at the infusion site can be prevented by the use of a central catheter for infusion.[117] Infusion reactions (<2% infusions) include flushing, urticaria, bronchospasm, facial swelling and pruritis,[39,143,144] but can be prevented by slowing the infusion and giving diphenhydramine. It appears from clinical trials (see section 7) that caspofungin has a higher propensity to cause histamine-induced reactions than the other echinocandins.[19] For anidulafungin, histamine-release symptoms are rare if the infusion rate does not exceed the maximum rate of 1.1 mg/min.[13] It may be that certain structural alterations in the cyclic hexapeptide core of the echinocandins influences their ability to cause histamine release. Compounds with a high proximal positive charge density have demonstrated high histamine-releasing potential in mouse models,[145] but this theory has not been tested with the echinocandins. Fever, rash, nausea and headache are uncommon for all three agents.[39,143,144,146,147] The most common adverse reactions in patients receiving the echinocandins in clinical trials are summarized in table V. The prescribing information for micafungin[12] contains additional cautionary notes with regard to possible haematological effects (e.g. acute intravascular haemolysis) and renal effects (elevations in serum creatinine levels and acute renal failure).

The extent to which the echinocandins cause liver toxicity is not clear. In early studies, liver enzymes were increased in volunteers receiving caspofungin in combination with ciclosporin. Subsequent retrospective analyses have failed to

Table V. The more common adverse reactions reported in clinical trials (expressed as a percentage of all adverse reactions)[11-13]

Adverse reaction	Caspofungin (%)	Micafungin (%)	Anidulafungin (%)
Pyrexia	21.2	Not documented	0.7
Diarrhoea	14.9	2.1 [gastrointestinal disorders (57.2)]	3.1 [nausea (1)]
Increased liver enzymes	ALT (14.9); AST (12.5); alkaline phosphatase (12.1)	Rare	ALT (2.3); γ-glutamyl transferase (1.3)
Hypokalaemia	11.8	1.8	3.1
Infusion-related reactions	2	45.6	Not documented
Metabolism and nutrition disorders	Not documented	42.7	Not documented
Headache	Not documented	Not documented	1.3
Neutropenia	Not documented	Not documented	1.0

show an increase in hepatoxicity with this combination.[148,149] Clinical trials with all three agents have revealed increases in liver enzymes, but in most cases they were as frequent in the comparator polyene or azole arm.[39,143,144] Whilst it is prudent to assess liver enzymes throughout the course of echinocandin therapy, concerns about hepatoxicity should not preclude their use.

7. Clinical Indications and Efficacy

The three echinocandins differ in the indications for which they are licensed, based on the clinical trial data available for each drug. Caspofungin is FDA approved for the empirical treatment of fever and neutropenia, for candidaemia and selected other forms of IC, oesophageal candidiasis and for IA refractory to other treatments or where there is intolerance to other agents. Micafungin and anidulafungin are licensed for the treatment of candidaemia, IC and oesophageal candidiasis, with micafungin additionally indicated for the prophylaxis of *Candida* infections in stem cell transplantation (SCT). These indications and the doses of the relevant echinocandin used in each indication are shown in table VI. Of note, a loading dose is not required for micafungin. The clinical evidence supporting these indications is discussed in the following subsections.

7.1 Antifungal Prophylaxis

The use of echinocandins in antifungal prophylaxis has been studied in the setting of SCT,

liver transplantation and following surgery. Additional studies are needed to determine their role in the prophylaxis of IFIs in other high-risk populations.

There has been one large double-blind randomized controlled trial (RCT) comparing micafungin 50 mg/day and fluconazole 400 mg/day as prophylaxis in neutropenic adults and children following autologous and allogeneic SCT.[147] Prophylaxis was continued until resolution of neutropenia and subjects were followed for 4 weeks thereafter. Success was defined as the absence of suspected, probable or proven IFI;[151] micafungin was found to be superior (success rate 80% vs 73.5% for fluconazole prophylaxis; p = 0.03). This difference was due largely to the difference in the number of patients with suspected IFI as defined by initiation of empirical antifungal therapy. There was no difference in mortality between the two groups. A smaller RCT of 104 SCT recipients also compared micafungin (150 mg/day) with fluconazole (400 mg/day) for prophylaxis; however, no difference in the prevention of IFIs was detected.[152] In a retrospective analysis of SCT recipients receiving caspofungin prophylaxis (35–50 mg/day; median duration 73 days), breakthrough IFI occurred in 7.3% of patients; the majority of these were due to moulds, diagnosed at a median of 65 days after starting prophylaxis.[153] These findings suggest that both micafungin and caspofungin are valuable options for antifungal prophylaxis in SCT recipients; however, candidiasis treatment guidelines only recommend micafungin for this indication.[14]

Table VI. US FDA-approved indications, dosing and costs of the echinocandins

Indication	Daily dose		
	caspofungin	micafungin	anidulafungin
Empirical treatment in febrile neutropenia	70 mg loading dose then 50 mg daily	NA	NA
Candidaemia	70 mg loading dose then 50 mg daily	No loading dose, 100 mg daily	200 mg loading dose then 100 mg daily
Other *Candida* infections[a]	70 mg loading dose then 50 mg daily	No loading dose, 100 mg daily	200 mg loading dose then 100 mg daily
Invasive aspergillosis in patients refractory of or intolerant to other therapies	70 mg loading dose then 50 mg daily	NA	NA
Oesophageal candidiasis	No loading dose, 50 mg daily	No loading dose, 150 mg daily	100 mg loading dose then 50 mg daily
Prophylaxis against *Candida* in SCT	NA	50 mg daily	NA
Paediatric patients aged ≥3 months	70 mg/m^2 (maximum daily dose 70 mg) then 50 mg/m^2 (maximum daily dose 70 mg)	NA	NA
Cost ($US)[b]	421.06 (70 mg vial) 405.25 (50 mg vial)	112.20 (50 mg vial) 224.40 (100 mg vial)	108.00 (50 mg vial) 216.00 (100 mg vial)
Cost (Australian dollars)[c]	724.63 (70 mg vial) 631.17 (50 mg vial)	889 (50 mg vial)	347.50 (50 mg vial) 695.00 (100 mg vial)
Infusion time	Over 1 h	Over 1 h	Not to exceed 1.1 mg/min (90 min for 100 mg dose)

a Caspofungin is approved for intra-abdominal abscesses, peritonitis and pleural space infections; micafungin is approved for acute disseminated candidiasis, abscesses and peritonitis; anidulafungin is approved for intra-abdominal abscesses and peritonitis.

b Cost represents average wholesale price obtained using the *Red Book*.[150]

c Australian market prices.

NA = not FDA approved; **SCT** = stem cell transplantation.

Mattiuzzi et al.[154] compared the efficacy of itraconazole 200 mg/day with caspofungin 50 mg/day for prophylaxis in 192 patients undergoing induction chemotherapy for acute myeloid leukaemia/myelodysplasia. The proportions of patients developing an IFI or persistent fever, or pulmonary infiltrates, were similar in both study arms. Caspofungin has also been evaluated in a small number of patients in the setting of 'secondary antifungal prophylaxis' during SCT. Two of 18 patients with IFIs in one study developed progressive disease while receiving the agent after transplantation.[155]

Liver transplant recipients at particularly high risk for IFI include those who require retransplantation due to graft dysfunction, renal replacement therapy within 30 days of first transplantation, and those with prior fulminant hepatitis, increased transfusion requirements and positive surveillance cultures for *Candida*;[156] this population is estimated to have a 20% incidence of IFI without prophylaxis. A prospective open-label study evaluated the efficacy of caspofungin 50 mg/day (given for at least 21 days) in such high-risk recipients.[59] The drug was started a median of 5 days after transplantation. Of 71 patients, 2.8% developed an IFI 19–41 days after cessation of caspofungin. Caspofungin was well tolerated. Finally, a noncomparative study of antifungal prophylaxis using caspofungin 50 mg/day in surgical patients at high risk (estimated risk 30–40%) for intra-abdominal IC, e.g. those with recurrent gastrointestinal perforation, has been undertaken.[157] Caspofungin was continued until resolution of the surgical condition. One breakthrough infection occurred in each of 19 patients.

7.2 Empirical Therapy in Febrile Neutropenia

Only caspofungin has been studied in a large-scale double-blind RCT for febrile neutropenia (table VI).[158] This noninferiority study of over

1000 patients found caspofungin to be better tolerated but equally as effective as liposomal amphotericin B (3 mg/kg/day) in patients with persistent neutropenic fever. Kubiak et al.[159] evaluated the safety and efficacy of caspofungin 50 mg/day or micafungin 100 mg/day in two consecutive cohorts receiving empirical therapy for febrile neutropenia: 323 patients received two or more consecutive doses of echinocandin. Adverse events requiring discontinuation of the echinocandin were infrequent (1–2%) in both groups and efficacy was similar with regard to death, breakthrough IFI and successful treatment of baseline IFI. Although not a randomized study, both drugs performed similarly in this group of patients.

7.3 Oesophageal Candidiasis

All three echinocandins are effective for the treatment of oropharyngeal and oesophageal candidiasis (table VI). To date, three RCTs have compared their efficacy (i.e. caspofungin, micafungin or anidulafungin) to that of fluconazole for oesophageal candidiasis;[160-162] the clinical responses to the study echinocandin and fluconazole were similar. However, in the studies involving caspofungin and anidulafungin, the relapse rate was higher in the echinocandin arm at 2–4 weeks of follow-up.[160,162] A randomized double-blind study comparing caspofungin at three different doses (35, 50 or 75 mg daily) to amphotericin B (0.5 mg/kg daily) in mostly HIV-infected patients[163] demonstrated similar favourable response rates for both arms. In an open-label study of anidulafungin, Vazquez et al.[164] evaluated the

response of azole-refractory mucosal candidiasis in 19 HIV-infected individuals treated with a 200 mg loading dose followed by 100 mg/day for 14–21 days. Clinical success was achieved in 95%, and endoscopic success in 92%, of patients, although clinical success had reduced to 47% at follow-up.[164]

7.4 Invasive Candidiasis

There are five key clinical trials of the treatment of candidaemia and other forms of IC with the echinocandins; all were double-blind RCTs (table VII).[39,143,144,165,166] Three RCTs[39,143,144] compared the efficacy of caspofungin, anidulafungin or micafungin with either amphotericin B, fluconazole or liposomal amphotericin B. In all cases, equivalent global favourable response, as defined by clinical resolution of candidiasis and microbiological eradication of infection, was demonstrated between the two study arms. In the studies involving anidulafungin and caspofungin[39,143] (comparator agents fluconazole 800 mg initially and then 400 mg daily, and amphotericin B deoxycholate 0.6–1 mg/kg daily, respectively; table VII), there was a suggestion of better outcomes in the echinocandin group but this was not significant based on analysis of the respective primary endpoints. The global response at the end of treatment using anidulafungin was 75.6% compared with 60.2% with fluconazole (p > 0.05),[39] whilst the efficacy was 73.4% for caspofungin (vs 61.7% for amphotericin B; p = 0.22).[143] Where an amphotericin B-based formulation was the comparator agent,

Table VII. Key clinical studies of echinocandins in candidaemia and invasive candidiasis

Agent and dosing	Comparator	No. of patients evaluated	Favourable outcome	Reference
Caspofungin 70 mg then 50 mg daily	Amphotericin B deoxycholate 0.6–1 mg/kg daily	224	73.4% vs 61.7%	143
Caspofungin 70 mg then 50 mg daily	Caspofungin 150 mg daily	197	71.6% vs 77.9%	165
Micafungin 100 mg daily	Micafungin 150 mg daily; caspofungin 70 mg then 50 mg daily	595	76.4% vs 71.4% 76.4% vs 72.3%	166
Micafungin 100 mg daily	Liposomal amphotericin B 3 mg/kg daily	392	89.6% vs 89.5%	144
Anidulafungin 200 mg then 100 mg daily	Fluconazole 800 mg then 400 mg daily	245	75.6% vs 60.2%	39

there was significantly less drug toxicity in the echinocandin arm.[143,144]

Two further studies have compared the efficacy of an echinocandin with higher doses of the same agent and/or higher doses of another echinocandin in IC.[165,166] Betts et al.[165] compared the efficacy of two doses of caspofungin – either an initial dose of 70 mg followed by 50 mg daily, or 150 mg daily without a loading dose – and found similar response rates of 71.6% and 77.9%, respectively. More adverse events were encountered with the higher dose of caspofungin, although this was not significantly different. In a three-armed study comparing micafungin 100 mg/day with micafungin 150 mg/day and with caspofungin, response rates were similar across all three arms.[165]

Several case reports have highlighted the successful use of caspofungin, with or without other antifungals, for uncommon or 'off-label' indications such as *Candida* endocarditis including that caused by non-*albicans Candida* spp. (reviewed by Eschenauer et al.[19]). These scenarios present an encouraging picture for the use of caspofungin, even as monotherapy, for therapy of fungal endocarditis. However, the echinocandins are not recommended for treatment of fungal brain abscesses or meningitis because of poor CNS penetration, although rare successes have been reported.[14,19] There are conflicting data concerning the use of caspofungin in the treatment of *Candida* endophthalmitis; however, on balance, echinocandins are not recommended in the primary treatment of *Candida* eye infections because the drugs do not penetrate appreciably into vitreous fluid.[14]

7.5 Invasive Aspergillosis

There are few data for the initial treatment of IA with echinocandins. Only caspofungin has been studied in this setting. Dignan et al.[167] examined an early treatment approach in high-risk SCT patients with possible IA[168] based on computed tomography scan findings suggestive of IA. Of 17 patients treated with caspofungin (75 mg loading dose then 50 mg daily), one developed a fatal *Aspergillus* infection. The efficacy

of caspofungin in the primary therapy of proven or probable IA[168] in patients with haematological malignancies has also been evaluated.[169] Of evaluable patients, 75% had cancer not in remission and 85% were neutropenic, a group with poor prognostic features. The response rate was 33% at the end of treatment. In another study (n = 24 patients), Herbrecht et al.[170] reported an efficacy of 33% at 12 weeks for caspofungin given as first-line therapy for proven/probable IA in allogeneic SCT recipients.

Both caspofungin and micafungin have been studied as salvage therapy for IA. Maertens et al.[171] prospectively evaluated caspofungin in 83 patients, most of whom were refractory to other therapies. An overall favourable response to caspofungin was noted in 45% of patients; response was 50% in those with IPA and 23% in patients with disseminated infection. Subsequently, these results have been compared with those from an historical cohort of 214 patients who received salvage therapies with amphotericin B formulations and/or itraconazole;[172] caspofungin was noted to be at least, and probably more, as effective as either amphotericin B formulations or itraconazole but the conclusions are limited by the retrospective nature of the comparison group. Smaller retrospective analyses of treatment responses to caspofungin in patients with IA in compassionate access schemes have shown response rates of 44–48%.[173,174] A prospective observational registry collected data about outcomes of caspofungin treatment for IA from 11 European countries.[175] Both data on initial treatment and salvage treatment were captured, with salvage therapy given in 82.4% of 103 patients; 82.5% of all patients received caspofungin monotherapy. Overall, a favourable response was seen in 56.4% of patients.

With regards to micafungin, a single open-label noncomparative study[176] was conducted to assess its safety and efficacy when used alone, and in combination with another antifungal agent in the primary or salvage therapy of IA. Favourable responses were achieved in 6 of 12 (50%) patients who received micafungin monotherapy as primary treatment and in 9 of 22 (40.9%) who received it as salvage therapy. Seventeen patients

received primary therapy with micafungin in combination with another agent, with a favourable response in five (29.4%); the response rate was 34.5% (60 of 174 patients) in instances of salvage therapy.[176] It should be noted that this study was conducted before the caspofungin salvage studies and without the benefit of harnessing *Aspergillus* galactomannan tests to support cases of 'probable IA', suggesting that patients may have had more advanced disease than those in the caspofungin study of Maertens et al.[171] In addition, the initial dose of micafungin employed was lower (75 mg/day, although this could be increased after day 5).

7.6 Combination Antifungal Therapy

The unique mechanism of the echinocandins has generated much interest in its use in combination antifungal regimens, particularly for IA. The clinical evidence in support (or not) of combination therapy employing various antifungal agents for different IFIs has been recently reviewed,[177] yet there are no RCTs examining the efficacy of combination antifungal therapy. The first RCT of combined voriconazole and anidulafungin, in comparison with voriconazole alone, in high-risk haematology patients is currently underway.[178] Clinical studies addressing combination antifungal therapies are difficult to interpret and have provided conflicting results as to the value of using drugs in combination. Data from small case series have largely used historical controls as comparisons or observational cohorts with few subjects having proven or probable IFIs, and have employed different methodologies.[179] Data are mostly limited to patients with haematological cancers and SCT recipients.

One small open-label pilot study compared liposomal amphotericin B (3 mg/kg/day) combined with caspofungin (50 mg/day) with liposomal amphotericin B monotherapy (10 mg/kg/day) in haematological patients with proven or probable IA.[180] Of 30 patients, at the end of treatment there were significantly more complete or partial responses in the combination arm: 67% versus 27% (p = 0.028). Survival was better in patients receiving combination therapy but this was not significant. In another noncomparative study, caspofungin in combination with one other mould active antifungal agent (investigator-chosen) was used for salvage therapy in 53 adults with proven or probable IA.[181] Patients received combination therapy for at least 28 days. Complete or partial response at the end of treatment and at day 84 after initiation of therapy was 55% and 49%, respectively. Agents used in combination with caspofungin were voriconazole, a polyene or itraconazole. Two other small retrospective studies of caspofungin-liposomal amphotericin B combination therapy in haematological patients reported similar favourable response rates (60–65%) at the end of therapy,[182,183] whilst another study reported improved survival from IA compared with historical controls when caspofungin and voriconazole were used as salvage in SCT recipients, although survival was no different at 1 year of follow-up.[184]

Micafungin has also been used in combination with other antifungal agents as salvage therapy in 194 patients with proven IA between 1998 and 2002, many of whom were SCT recipients.[176] The response rate was 34.5% but many of these patients likely had advanced disease compared with patients in more recent studies and the initial dose of micafungin employed was low at 75 mg. A response rate of 24% has also been reported in a subset of 90 SCT patients with IA who received combination micafungin-liposomal amphotericin B therapy in mostly refractory infection, although the same caveats about advanced infection and a low initial dose of micafungin apply.[185] One cohort of solid organ transplant patients who prospectively received combination caspofungin and voriconazole treatment were compared with a historical control group receiving liposomal amphotericin B. Successful outcomes were seen in 70% of patients receiving combination therapy (vs 51% on liposomal amphotericin B), albeit without survival difference.[186]

7.7 Clinical Studies in Children

Caspofungin and micafungin have been studied in children for the treatment of febrile neutropenia, antifungal prophylaxis for SCT

recipients and treatment of IFIs. Details of published clinical data for therapeutic use are detailed in a recent review.[22] To date, there are no published clinical trials of anidulafungin in children.

7.7.1 Antifungal Prophylaxis

Micafungin is the only echinocandin that has been evaluated for fungal prophylaxis in paediatric SCT recipients. In a study by Van Burik et al.[147] (see section 7.1), micafungin was as effective at preventing IFIs, and more protective than fluconazole against aspergillosis in children undergoing SCT despite the limited number of children evaluated (10% of all patients). Other small studies of micafungin (either open-label or compared with a fluconazole prodrug) in children with haematological disease[187,188] have also indicated low rates of IFI and that micafungin was safe to use. One very recent study has provided data to indicate that alternate day micafungin prophylaxis may be feasible in children aged ≤10 years.[189]

7.7.2 Febrile Neutropenia

Only caspofungin has been evaluated for the treatment of paediatric febrile neutropenia. One RCT compared the efficacy of caspofungin (50 mg/m^2) and liposomal amphotericin B (3 mg/kg/day) in 82 children aged 2–17 years. Efficacy and safety were similar for both study arms as was noted in a similar study in adults.[158,190] In addition, Koo et al.[191] retrospectively reviewed 56 children aged 1–17 years with febrile neutropenia treated empirically with caspofungin. Of 67 courses of therapy, successful treatment of baseline fungal infection was reported in 79%, with no breakthrough IFIs. Adverse events possibly related to caspofungin occurred in 13% of courses.

7.7.3 Invasive Candidiasis, Invasive Aspergillosis and Other Invasive Fungal Infections

It was only recently that the landmark study leading to the FDA approval of caspofungin for use in children was published. Zaoutis et al.[192] conducted an open-label prospective study of caspofungin for the treatment of *Candida* and *Aspergillus* infections in patients aged 3 months to 17 years. Of 48 patients with proven infections,

10 had IA, 37 IC and 1 had oesophageal candidiasis. Success (defined by complete or partial response) at end of therapy was seen in 5 (50%) patients with IA and 31 (81.1%) with candidiasis. However, patients with candidiasis were more likely to have been treated for primary infections, whereas all children with IA had failed to respond to other antifungals. There were no serious drug adverse events. While the results of this trial support caspofungin safety and efficacy in IFIs in children, it was a nonblinded noncomparative study with a small patient population.

Prior to this study, published data on the use of caspofungin in children had largely been limited to neonatal candidiasis,[193,194] although its use in managing IC was retrospectively described within larger paediatric cohort studies.[195] Experience with salvage caspofungin treatment in neonatal candidiasis was reported in a prospective case series of ten children (mean birthweight 1500 g).[193] Eight children with persistent candidaemia cleared their infection after a mean of 4.3 days of caspofungin, one child had relapsed candidaemia within 4 days of stopping caspofungin and one with disseminated infection responded but died from bacterial sepsis. No adverse drug events were noted. In another study, 11 of 13 neonates with persistent candidaemia cleared their infection with caspofungin.[194]

The largest paediatric micafungin trial was an RCT substudy in 98 children with IC.[196] Patients received micafungin or liposomal amphotericin B for ≥14 days. Success (clinical and mycological response) rates were similar between the two groups (72.9% and 76.5%, respectively). The study was not powered to detect differences among different age cohorts. An open-label multicentre trial[197] evaluated micafungin alone or in combination for new and refractory candidaemia. Of 20 children in the study, 15 (75%) were treated successfully.

Echinocandins have also been specifically studied in acute paediatric IA. As discussed in section 7.5, the largest prospective study was with micafungin (75 mg daily but allowing dose escalation) alone or in combination with another antifungal agent.[176] Of 58 children treated, the success rate at the end of therapy was 44.8% (26 patients).

Two smaller studies have evaluated caspofungin in combination therapy. One reviewed 40 children enrolled in a haematology-oncology registry given (mainly) salvage antifungal combination therapy for proven/probable IA[198] and included those treated with caspofungin (70 mg/m^2 on day 1 then 50 mg/m^2 daily) in combination with another agent, usually liposomal amphotericin B or voriconazole. Complete or partial responses were seen in 21 (53%) patients with an overall 8-month survival of 50%.[198] Limitations of this study include few patients with primary infections. A smaller study of immuncompromised children with refractory IFI treated with caspofungin-liposomal amphotericin B combination noted complete responses for five of nine patients.[199]

8. Costs

The cost of antifungal drugs and, perhaps more importantly, estimates of the cost benefit of selected therapeutic regimens (prophylaxis, pre-emptive, empirical or organism-directed therapy) in specific settings (e.g. the ICU, haematology patients) are of increasing importance in clinical practice. The echinocandins are expensive agents. At existing prices (table VI), the cost of treatment is likely to remain an important consideration for management. Comparative estimates of cost efficacy between echinocandins, and between echinocandins and other antifungal drugs, have been developed using decision-analytic and other methodologies, but the outcomes are not necessarily generalizable because of the incorporation of different parameters and including administrative expenses into the respective models.

In a single head-to-head comparison of micafungin and caspofungin in the treatment of IC in the UK, there was no significant difference in cost efficacy between the two.[200] Other studies have modelled the cost efficacy of an echinocandin compared with liposomal amphotericin B for empirical therapy for febrile neutropenia and suspected IFI[201-203] and have consistently reported a cost benefit in favour of the echinocandin. In one study, using a model that included successful fever resolution, cure of baseline infection, absence of breakthrough infection, sur-

vival and quality-adjusted life-years as endpoint parameters, the effectiveness of caspofungin (70 mg on day 1 followed by 50 mg/day) over liposomal amphotericin B (3 mg/kg daily) was demonstrated.[203] The average total direct cost based on drug costs in 2005 favoured the use of caspofungin (£9763 vs £11 795). However, total costs depend on the dose of liposomal amphotericin B used in different clinical settings and of the need for higher caspofungin doses in patients weighing >80 kg (70 mg/day). Micafungin was reported to be more cost effective than fluconazole in an ICU population with sepsis; in this study, the benefit was predicated on the emergence of fluconazole-resistant *Candida* spp.[204] In a pharmaceutical company-funded study in Korea, micafungin prophylaxis was associated with the more cost-effective and better outcomes than fluconazole in SCT recipients.[205] Confirmation of these findings in independent studies is awaited.

Importantly, published prices are driven by local market prices, making a generalized economic analysis difficult because of disparity in drug prices between regions (table VI). For example, the direct cost of anidulafungin is substantially greater in Australia than in the US. At this time, echinocandins appear to be of equivalent efficacy and cost effectiveness.

9. Conclusions

The echinocandins are a valuable addition to the present-day antifungal armamentarium for the treatment of IFIs. Although they have a narrow antifungal spectrum, these agents cover the two most common IFIs, candidiasis and aspergillosis. As a class of antifungal agent, they are safe, well tolerated, and demonstrate favourable pharmacokinetic and pharmacodynamic profiles. Further studies are required to determine dosing in obese patients and children, and exploration of the role of intermittent dosing strategies, including cost-efficacy analyses, which would make the echinocandins appealing for outpatient use.

There are differences among the three echinocandins with respect to half-life, metabolism, requirements for a loading dose (not needed with micafungin), time to steady state and drug

interaction profile. Anidulafungin is the only agent that does not have known clinically significant drug interactions, including with immunosuppressive agents. This agent may have lower MICs against certain *Candida* strains that are considered non-susceptible to caspofungin or micafungin,[54] and may influence the choice of agent. However, on balance, the echinocandins do not appear to demonstrate any differences in clinical efficacy in the disease entities that have been studied and it is unlikely that any one agent would be found to be clearly superior with regard to clinical outcome.

Other characteristics that distinguish the echinocandins include FDA-approved indications. Only micafungin is licensed for antifungal prophylaxis in SCT, whereas capsofungin is the only agent approved for IA in patients intolerant of or refractory to other therapies, and in the empirical treatment of presumed IFI in febrile neutropenic patients. However, the fact that echinocandins do not have activity against fungi other than *Candida* and *Aspergillus* spp. should be kept in mind when selecting empirical antifungal therapy in severely immunocompromised patients. Currently, their major niche is in the treatment of serious candidal infections, especially candidaemia. One therapeutic strategy that should be explored is where a patient with IC is initially treated with an echinocandin and then switched to an azole, preferably in oral form, after the patient has had a clinical response and the results of species and/or antifungal susceptibility data are available. Although RCT data do not exist for any of the echinocandins at present, *in vitro* and animal infection data for the primary treatment of IA indicate that all three drugs would be comparable in this setting. Combination therapy trials incorporating the echinocandins are urgently needed, especially in the treatment of IA.

The echinocandins are expensive to use. Clinicians' choice regarding which agent to choose will likely be driven by pharmacoeconomics rather than efficacy or toxicity. At present, unless substantially subsidized, no single echinocandin agent is likely to have a decisive advantage over the others.

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Correspondence: Assistant Professor *Sharon Chen*, Centre for Infectious Diseases and Microbiology, 3rd Level, ICP&MR Building, Westmead Hospital, Darcy Road, Westmead, NSW 2145, Australia.
E-mail: sharon.chen@swahs.health.nsw.gov.au