



# Anidulafungin: a novel echinocandin

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Fungal infections have emerged as a major cause of morbidity and mortality in an immunocompromised host. Until recently, the available treatment for serious fungal infections comprised either amphotericin B or azoles, which have limitations. The development of the echinocandins, including caspofungin and micafungin, has helped to fill the need for more efficacious antifungals that are broad spectrum, useful across different patient populations and have a good safety profile. Anidulafungin is the newest of the echinocandins under development for the treatment of mucosal and systemic fungal infections. Anidulafungin has demonstrated potent *in vitro* activity against *Aspergillus* and *Candida* spp., including those strains that are resistant to either fluconazole or amphotericin B. Results of several clinical trials show that anidulafungin is effective in treating esophageal candidiasis, candidemia and invasive candidiasis. In addition, studies evaluating the concomitant use of anidulafungin and either amphotericin, voriconazole or cyclosporin did not show clinically significant drug–drug interactions or altered adverse event profiles. A population kinetics analysis showed no significant effect of age, race, concomitant medications and renal or hepatic insufficiency on the population kinetic properties of anidulafungin. The efficacy and safety profile of anidulafungin, combined with its unique pharmacokinetic characteristics, make it a suitable alternative antifungal compound for first-line therapy of candidemia as well as mucosal, systemic and antifungal-refractory candidiasis.

Invasive fungal infections are a major and growing cause of morbidity and mortality in immunocompromised patients. Over the past 25 years, the incidence of invasive fungal infections has increased markedly [1]. From 1980 to 1987, mortality increased 3.4-fold, up from 0.7 to 2.4 deaths/100,000 population [1].

Individuals at high risk for serious fungal infections include patients with HIV/AIDS, patients in either medical or surgical intensive care units; surgical patients, those with hematologic malignancies (e.g., leukemia and lymphoma) and those with solid tumors [1–4]. In addition, patients undergoing solid-organ or hematopoietic stem cell transplantation, especially those in whom graft versus host disease or cytomegalovirus infection develops or who are exposed to corticosteroids, are also at high risk of developing and dying from invasive mold infections, such as systemic aspergillosis or fusariosis [5–8].

Besides systemic infections, oropharyngeal (OPC) and esophageal candidiasis (EC) are also very common opportunistic fungal infections in patients with HIV, diabetes and those on corticosteroids. Among patients with HIV/AIDS, up to 90% will experience an episode of OPC during

their lifetime [2–4]. In addition, approximately 10% of HIV-infected patients will experience an episode of EC at some time during the course of their disease [3,4].

The epidemiology of invasive fungal infections has also changed substantially over the past decade [9–11]. Although *Candida* spp. are still the most common cause of fungal infections among compromised hosts, in many tertiary-care institutions for transplant recipients or patients with hematologic malignancies, *Aspergillus* has become a leading cause of morbidity and mortality, affecting as many as 30% of patients [6,7]. Recently, the distribution of *Candida* species producing systemic invasive infections has also shifted. For many years, *Candida albicans* was the primary cause of mucosal and systemic infections [9–11]. During an active-surveillance study, *C. albicans* comprised only 45% of *Candida* isolates recovered from hospitalized patients [10]. In this study, the incidence of non-*albicans Candida* species experienced a dramatic increase in frequency, especially with *Candida glabrata*, *Candida parapsilosis* and *Candida tropicalis*, all of which are generally less susceptible to conventional antifungal agents [9–14]. In a multi-center study of 1471 high-risk patients,

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*C. albicans* was the most common bloodstream isolate, recovered in 45 and 49% of adults and children, respectively. Candidemia due to *C. albicans* was associated with mortality rates of 47 and 29% in adults and children, respectively [14]. Despite newer therapeutic modalities and improved medical care in intensive care units, candidiasis and candidemia are still associated with extremely high mortality rates [14].

There are substantially fewer antifungals than there are antimicrobials. Thus, there remains a significant need for more effective antifungals, since conventional agents, such as amphotericin B and the azoles, continue to have problems with administration intolerance and severe adverse events. Nephrotoxicity remains a major concern with amphotericin B and its lipid formulations, while drug interactions, hepatotoxicity and skin reactions continue to affect the azole antifungals [13,15–17].

Echinocandins are a new class of antifungal that have shown extremely good results in numerous clinical trials and for a variety of fungal infections, including invasive infections due to either *Candida* or *Aspergillus*. Thus far, these antifungals have shown excellent clinical efficacy and a more favorable adverse-event profile when compared with conventional antifungal agents [18–21]. Anidulafungin is the newest agent

in the echinocandin family of antifungals that are being developed for the treatment of mucosal and systemic fungal infections (Figure 1) [21].

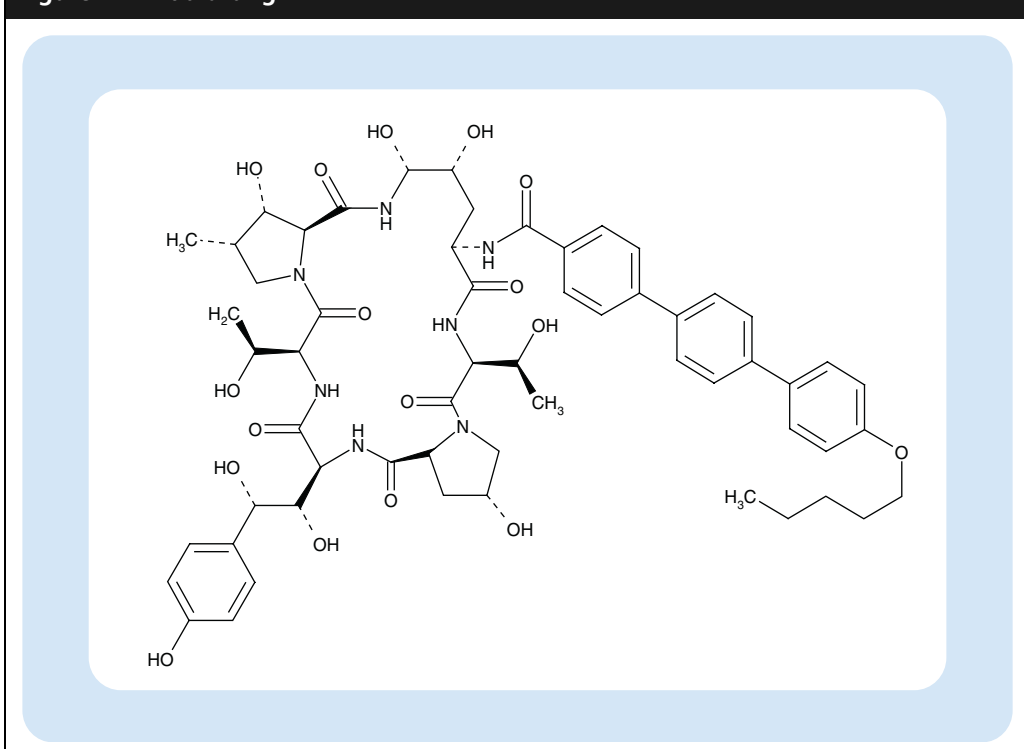
### Pharmacodynamic properties

Anidulafungin is a semisynthetic lipopeptide synthesized from the fermentation products of *Aspergillus nidulans*. The compound is a non-competitive inhibitor of  $\beta$ -1,3-D-glucan synthase, resulting in the selective inhibition of the synthesis of glucan [20,21]. Glucan, a major structural component of the cell wall of many pathogenic fungi, is not present in mammalian cells and therefore may offer a selective target for the echinocandins antifungals [20,21].

### In vitro analyses

Anidulafungin has potent fungicidal activity *in vitro* against a broad range of *Candida* species and fungistatic activity against many *Aspergillus* species [22–35]. This includes *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *Candida famata*, *Candida rugosa*, *Candida stellatoidea*, *Candida krusei* and *Candida lusitanae* (Table 1) [22–32]. The minimum inhibitory concentration (MIC) of anidulafungin against *Candida* species is in the range of approximately 0.03 to 4  $\mu$ g/ml. In addition, anidulafungin is active *in vitro* against *Candida* species that are shown to be resistant to

Figure 1. Anidulafungin.



**Table 1. *In vitro* activity of anidulafungin against *Candida* spp.**

Study/species	No. of isolates	MIC range ( $\mu\text{g/ml}$ )	MIC <sub>50/90</sub> ( $\mu\text{g/ml}$ )
<i>Candida albicans</i>	413	$\leq 0.03$ –0.25	0.125/0.25
<i>Candida glabrata</i>	275	$\leq 0.03$ –1	0.25/0.5
<i>Candida lusitanae</i>	10	0.125–2	0.5/2
<i>Candida parapsilosis</i>	28	0.12–2.0	2/4
<i>Candida tropicalis</i>	58	0.06–2	0.25/0.5
<i>Candida krusei</i>	36	0.12–1.0	0.25/0.5
<i>Candida guilliermondii</i>	9	1–4	4

MIC: Minimum inhibitory concentration; MIC<sub>50/90</sub>: Minimum concentration that is inhibitory for 50 or 90% of all isolates.

Adapted from [22,29,32].

azoles (*C. krusei*), amphotericin B (*C. lusitanae*) or caspofungin (*C. parapsilosis*) [24,30,32–34,36–38].

Compared with other antifungal agents, such as caspofungin and amphotericin B (MIC<sub>90</sub>: 0.25 and 1.0  $\mu\text{g/ml}$ , respectively), anidulafungin (MIC<sub>90</sub>:  $\leq 0.03$   $\mu\text{g/ml}$ ) has shown significant *in vitro* activity against several different species of *Aspergillus* including *A. fumigatus* (Table 2) and others [26,30,35,36]. In addition, additive effects and synergistic activity have been observed *in vitro* with anidulafungin and amphotericin B against *Aspergillus* and *Fusarium* isolates [39]. Synergistic activity was also found when anidulafungin was combined with itraconazole or voriconazole against *Aspergillus* [40]. Anidulafungin has also been shown to have *in vitro* activity against select molds, such as *Bipolaris spicifera*, *Exophiala jeanselmei*, *Fonsecaea pedrosoi*, *Madurella* spp., *Penicillium marneffeii*, *Phialophora verrucosa*, *Pseudallescheria boydii* and *Wangiella dermatitidis* [36]. Although anidulafungin is considered a broad spectrum antifungal, it has shown poor activity against *Cryptococcus neoformans*, *Fusarium* spp., *Trichosporon asahii* and the *Zygomycetes*. In all probability, this is due to its mechanism of action and the fact that these fungi have decreased glucan content in their cell walls [20,21].

### Resistance

*In vitro* resistance to anidulafungin is extremely rare [20,21,40]. However, there has been one published case report that describes the development of caspofungin and micafungin resistance *in vivo*, in a patient with prosthetic valve endocarditis due to *C. parapsilosis* [37]. The patient was initially treated with simultaneous caspofungin and fluconazole for a 6-week course of antifungal therapy without removing the infected prosthetic heart valve. The case is unique as the secondary

development of caspofungin and micafungin cross-resistance, with MIC values increasing to greater than 16  $\mu\text{g/ml}$ , while the isolates remained susceptible to anidulafungin (MIC: 2  $\mu\text{g/ml}$ ).

Echinocandins are relatively new and reports of resistance are rare; thus, the mechanism of resistance remains unknown. At this point, the use of echinocandins does not appear to lead to the development of cross-resistance to other antifungals such as polyenes or azoles. Although it is still too early to be certain, the possibility of echinocandin cross-resistance appears to be a viable possibility.

### In vivo analyses

Several animal models for evaluating the efficacy and tolerability of anidulafungin against yeast and mold infections have been developed. In a dose-ranging study comparing anidulafungin, fluconazole and amphotericin B in immunosuppressed rabbits with EC due to fluconazole-resistant *C. albicans*, treatment with anidulafungin showed a significant dose-dependent clearance of *C. albicans* from all sites (tongue, oropharynx, esophagus, stomach and duodenum;  $p < 0.05$ ) [38]. In contrast, treatment with amphotericin B resulted in a decrease in colony-forming units (CFUs) in only the tongue. Anidulafungin-treated animals had no detectable elevations in hepatic enzymes, alkaline phosphatase, bilirubin, potassium or creatinine [38]. The pharmacokinetic properties of anidulafungin have also been evaluated in a neutropenic rabbit model with subacute disseminated candidiasis [41]. This study showed a dose-dependent clearance of *C. albicans* CFUs from the kidneys with anidulafungin at doses of 0.5 mg/kg/day or more ( $p < 0.001$ ) and a significant improvement in survival at doses of up to 20 mg/kg/day ( $p < 0.05$ ) [41].

**Table 2. *In vitro* activity of anidulafungin, amphotericin, caspofungin, itraconazole and voriconazole against *Aspergillus fumigatus*.**

Drug	MIC <sub>50/90</sub> (µg/ml)
Anidulafungin	≤0.03/≤0.03
Amphotericin B	0.5/1
Caspofungin*	0.06/0.25
Itraconazole	0.06/0.12
Voriconazole	≤0.03/0.12

MIC<sub>50/90</sub>: Minimum concentration of agent that is inhibitory for 50% or 90% of all isolates.

\*Expressed as minimal effective concentration. Adapted from [35].

In a rabbit model of disseminated candidiasis treated with either anidulafungin (0.5 or 1 mg/kg/day), amphotericin B (1 mg/kg/day), or fluconazole (10 mg/kg/day), all groups showed similar degrees of *Candida* clearance from the liver, lung, spleen, vena cava, kidney and brain. Higher serum creatinine levels ( $p < 0.001$ ) and lower serum potassium levels ( $p < 0.01$ ) were noted in rabbits treated with amphotericin B when compared with fluconazole and anidulafungin [42].

In a separate study, anidulafungin (5 or 10 mg/kg/day) was associated with prolonged survival and reduced antigenemia in a rabbit model of disseminated aspergillosis [43]. In cultures from hepatic, pulmonary and renal tissues, treatment with anidulafungin was associated with a reduction in *A. fumigatus* colony size, from 0.5 to 1.5 cm before treatment to as small as 0.1 cm after treatment [43]. In a study evaluating the efficacy and tolerability of anidulafungin in an experimental model of invasive pulmonary aspergillosis in persistently neutropenic rabbits, survival improved and pulmonary injury decreased, with no evidence of toxicity [44].

### Pharmacokinetic properties

Anidulafungin is unique even among other echinocandins, as it degrades slowly in human plasma, undergoing a process of biotransformation rather than being metabolized [45,46]. As with caspofungin and micafungin, the compound is only administered intravenously. An initial loading dose of twice the daily dose achieves a level near steady state within 24 h after the first dose [47,48]. *In vitro* studies have shown that anidulafungin is protein bound (~84%) to human plasma (Table 3) [47,48].

### Degradation & elimination

The echinocandins consist of an amphiphilic hexapeptide ring with a lipid side chain that in anidulafungin is an alkoxytriphenyl chain [20].

More than 90% of anidulafungin undergoes a slow chemical degradation in the blood and does not involve the hepatic cytochrome P (CYP)450 system. Initially, it is degraded into an open-ringed product that is then degraded by non-specific peptidases into inactive compounds. As observed in both human and animal pharmacokinetic studies, the half-life of anidulafungin is approximately 24 h, whereas the half-life of the degradation products is approximately 4 days. Minimal drug or drug degradation products are found in the urine [46]. Most anidulafungin degradation products pass into the feces via the biliary tree [45,46]. The significance of this high degree of degradation instead of metabolism is important for anidulafungin's minimal drug–drug interaction profile.

### Special population pharmacokinetics

The pharmacokinetic properties of anidulafungin are similar across a variety of patient populations, suggesting that dose adjustments are not necessary. Hepatic and/or renal impairment have not been shown to affect anidulafungin clearance, indicating that anidulafungin would be well-tolerated patients with these conditions without dose adjustments (Table 3) [49–55]. In addition, dose adjustments would be expected to be unnecessary as suggested by a lack of variability in anidulafungin pharmacokinetic properties in a wide spectrum of mucocutaneous and invasive fungal infections, regardless of the patient's age, body weight, sex, race and severity of hepatic or renal dysfunction [52,54,55].

To evaluate the possible effects of demographic and clinical factors (e.g., age, body weight, sex, race, disease type and severity and concomitant administration of medications) on the pharmacokinetic properties of anidulafungin, a population model was constructed [52,55]. In four different Phase II/III clinical studies, anidulafungin's plasma clearance was determined based on levels from 600 plasma samples recovered from 225 patients who received anidulafungin at doses of either 50, 75 or 100 mg/day for EC (129 patients), IC (87), invasive aspergillosis (IA) (seven) andazole-refractory mucosal candidiasis (two) [48,52,55–57]. Anidulafungin was given in an initial loading dose that was twice the daily dose. Blood samples were collected after the third dose was administered to ensure a steady state had been reached. This model showed a difference in clearance rate of less than 20%, regardless of body weight, sex or disease type and severity, with enough overlap among categories

**Table 3. Pharmacokinetic properties of anidulafungin in healthy adults and special situations.**

Property	Value
C <sub>max</sub> (µg/ml)	3.5
C <sub>min</sub> (µg/ml)	2.0
Vd (l)	33.2
AUC <sub>0–24</sub> (µg/ml/h)	51
Protein binding (%)	84
Excretion pathway	>90% chemically degraded in the blood, bypasses hepatic metabolism, eliminated in feces
Renal excretion (%)	<1
Half-life (h)	25.6
Dosage*	100 mg on day 1, followed by 50 mg/day

\*Dosage is acceptable for all adults, including those receiving concomitant medications and/or with renal and/or hepatic impairment.  
 AUC: Area under the curve; C<sub>max</sub>: Maximum concentration;  
 C<sub>min</sub>: Minimum concentration; Vd: Volume of distribution.  
 Adapted from [46,52].

that the differences were deemed to have little clinical significance. Other variables, such as age, race and concomitant administration of various medications, were also found not to have a significant effect on anidulafungin clearance ( $p < 0.05$ ) (Figure 2) [52,54].

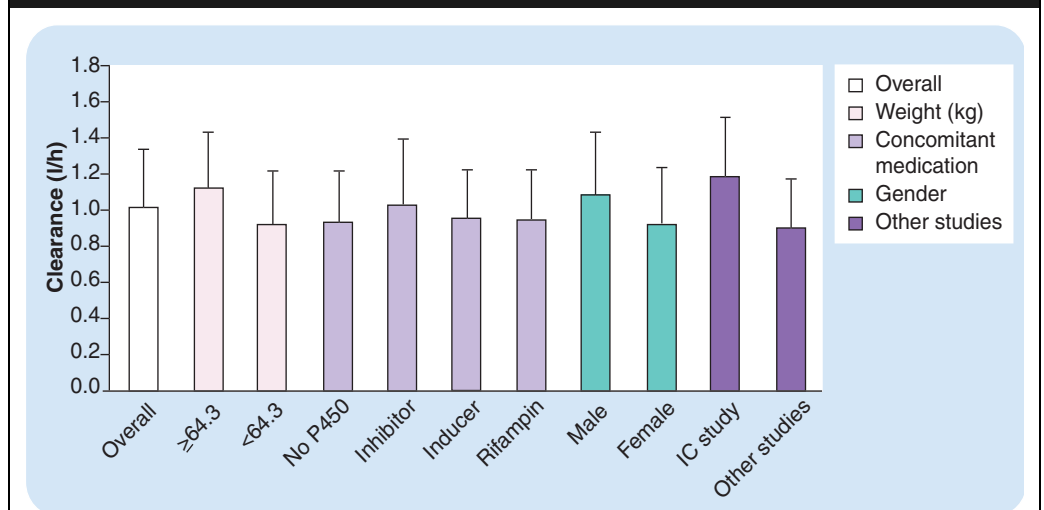
**Coadministration with medications affecting the cytochrome P450 system**

In the population pharmacokinetic study, anidulafungin clearance was not affected by concomitant treatment with substrates, inhibitors or inducers of

the CYP450 metabolic pathway, including rifampin (Figure 2) [52,54–56]. This is in contrast to the drug–drug interaction profile described for caspofungin, in which the coadministration of various agents that affect CYP450 isoenzymes, such as rifampin, dexamethasone and carbamazepine, have been shown to decrease the concentration of caspofungin, thus requiring higher doses of caspofungin (70 mg/day) when these drugs are given together [57,58].

The coadministration of voriconazole and anidulafungin was evaluated in healthy volunteers. In a randomized, blinded, crossover study evaluating the pharmacokinetic properties of anidulafungin when given concomitantly with voriconazole, the volunteers received the following three treatments in random sequence: anidulafungin (100 mg/day) plus voriconazole (200 mg every 12 h) on days 2 to 4; anidulafungin monotherapy (100 mg/day) on days 2 to 4; and voriconazole monotherapy (200 mg every 12 h) on days 2 to 4, with a 10-day washout period between treatment periods [59]. All study medications were given at a loading dose of twice the daily dose. To ensure that a steady state had been achieved, parameters were determined after the fourth dose of each treatment had been given. In the 17 men (age range, 20–40 years) who completed the study, the mean maximum concentration (C<sub>max</sub>) was 7.87 mg/l (area under the curve [AUC]: 120 mg/l/h) for anidulafungin monotherapy and 7.91 mg/l (AUC: 118 mg/l/h) for anidulafungin plus voriconazole, indicating a

**Figure 2. Anidulafungin clearance versus potential covariates, including cytochrome P450 substrates, inhibitors or inducers and rifampin.**



IC: Invasive candidiasis.  
 Adapted from [54].

lack of effect of concomitant voriconazole administration on the pharmacokinetic properties of anidulafungin [59].

The interaction of anidulafungin and cyclosporin has also been evaluated in healthy volunteers [60,61]. A total of 12 subjects aged 18 to 50 years received anidulafungin (100 mg/day) on days 2 to 8, following a loading dose of 200 mg on day 1 and cyclosporin (1.25 mg/kg twice daily) on days 5 to 8. Of these subjects, one was withdrawn on day 6 due to abnormal hepatic function test results ( $2 \times$  upper limit of normal [ULN]), which was considered possibly related to the study drugs. In the remaining 11 subjects, mean  $C_{\max}$  was statistically similar on days 4 (monotherapy) and 8 (coadministration) (7.5 and 8.1 mg/l, respectively). With the coadministration of cyclosporin, anidulafungin drug exposure increased by 22% overall (AUC: 104.5 mg/l/h [monotherapy] vs 127.6 mg/l/h [coadministration];  $p < 0.05$ ) [60]. Although the differences in these parameters were statistically significant, *in vivo* it was not clinically significant. In contrast, previous studies have shown an increase in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) up to  $3 \times$  ULN in subjects who received caspofungin and cyclosporin concomitantly [62]. In fact, two studies have shown that the concomitant administration of caspofungin and cyclosporin increase the caspofungin AUC by approximately 35%. It is possible that elevated ALT/AST levels are the result of increased caspofungin exposure [62]. The interaction of anidulafungin and tacrolimus has also been evaluated in healthy volunteers [63]. An open-label sequence pharmacokinetic interaction study was conducted in subjects aged 18 to 55 years. A total of 36 subjects received a 5-mg dose of tacrolimus on days 1 and 13, while 100 mg of anidulafungin was given intravenously on days 5 to 13. There were no dose-limiting toxicities and all treatment-related adverse events were considered mild and consistent with the known profiles of both drugs. The coadministration of anidulafungin and tacrolimus did not affect the pharmacokinetic parameters of either.

In a study in patients with invasive aspergillosis, anidulafungin (100 mg/day) and liposomal amphotericin B (LAMB) (5 mg/kg/day) were administered concurrently until the resolution of signs or symptoms of disease, or after 90 days of therapy [64]. The reported adverse events and laboratory abnormalities were not unexpected and found to be no worse with combination therapy compared with LAMB monotherapy in

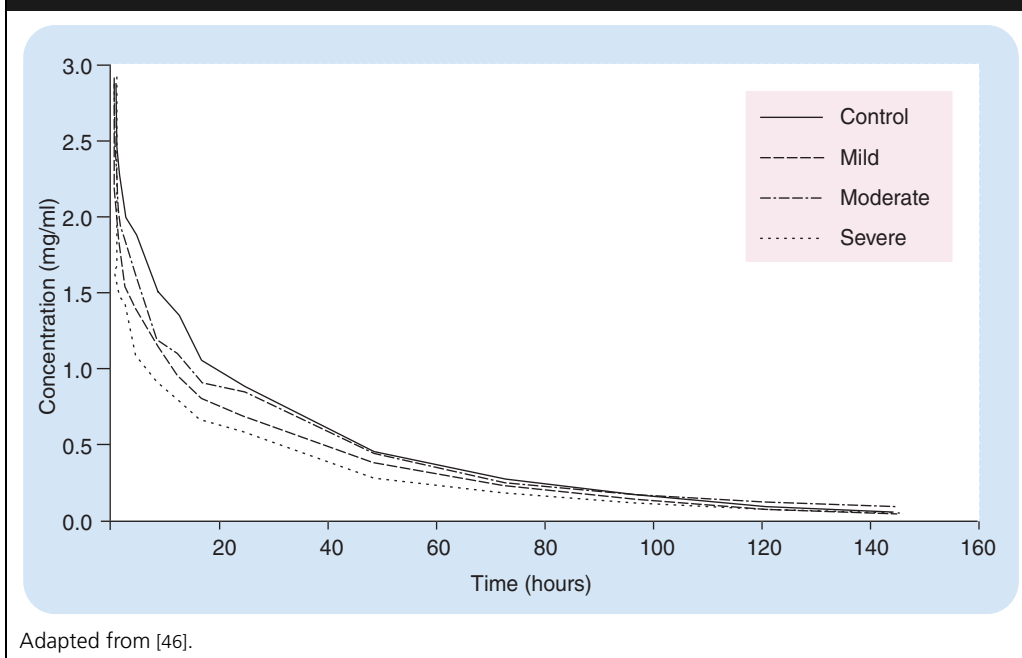
this population of 30 patients (age range: 21–79 years). In a separate study, a two-compartment pharmacokinetic model that described the steady-state properties of anidulafungin was established [56]. This model assessed patients with fungal infections who were receiving anidulafungin and LAMB concomitantly. In patients with invasive aspergillosis receiving concomitant LAMB, pharmacokinetic parameters were similar to parameters of patients with candidal infections who did not receive concomitant LAMB. Both groups of patients showed similar calculated values with regard to anidulafungin clearance, volume of distribution (Vd) at the steady state ( $AUC_{ss}$ ) and half-life.

#### Hepatic insufficiency

In a pharmacokinetic study evaluating a single-dose (50 mg) of anidulafungin in 24 individuals aged 18 to 75 years, the mean  $C_{\max}$  was 2.9 mg/l (AUC: 70.0 mg/l/h) in subjects with normal hepatic function, and 2.2, 2.3 and 1.8 mg/l in patients with mild (Child-Pugh class A), moderate and severe hepatic impairment, (AUC: 56.0, 68.6 and 46.6), respectively (Figure 3) [49].  $C_{\max}$  and AUC values in patients with mild or moderate impairment were statistically similar to those in normal subjects. These values were significantly lower in patients with severe hepatic impairment compared with normal controls ( $p < 0.05$ ); however, anidulafungin concentrations and exposures were within therapeutic ranges. In patients with severe hepatic impairment, the lower exposure compared with control subjects was considered secondary to ascites and edema and to be within the variability observed in normal subjects [49,51]. Consequently, anidulafungin dose adjustment has not been recommended for any degree of hepatic impairment.

#### Renal insufficiency

Based on the results of anidulafungin pharmacokinetic studies in patients with impaired renal function, dose adjustment is not needed. In a pharmacokinetic study of single-dose (50 mg) anidulafungin in 32 adults aged 18 to 75 years with normal or impaired renal function, mean  $C_{\max}$  was 2.1 mg/l (AUC: 51.1 mg/l/h) in those with normal renal function, 2.2 mg/l (AUC: 52.5 mg/l/h) in those with mild renal impairment (creatinine clearance [CrCl]: 51–79 ml/min), 2.7 mg/l (AUC: 61.4 mg/l/h) in those with moderate renal impairment (CrCl: 31–50 ml/min), 2.3 mg/l (AUC: 54.2 mg/l/h) in those with severe renal impairment (CrCl:  $\leq 30$  ml/min) and 2.2 mg/l (AUC:

**Figure 3. Serum anidulafungin concentrations in healthy subjects and patients with hepatic impairment.**

52.7 mg/l/h) in those with end stage renal disease (dependent on hemodialysis) (Figure 4) [53]. Other parameters (i.e., Vd, half-life and CrCl) were statistically similar among subjects [49,50,53].

#### *Pediatric populations*

In a study examining the pharmacokinetic properties of anidulafungin in 24 immunocompromised children aged 2 to 12 years, CrCl and Vd values were similar to those in adults, suggesting anidulafungin dose adjustments based on age may not be necessary in pediatric patients [65]. Differences in pharmacokinetic parameters were strongly correlated with body weight and could be addressed using a weight-adjusted dose. Preliminary analysis has shown similar pharmacokinetic parameters in pediatric patients receiving anidulafungin doses of 0.75 or 1.5 mg/kg/day and adults receiving either 50 or 100 mg/day.

#### **Clinical efficacy**

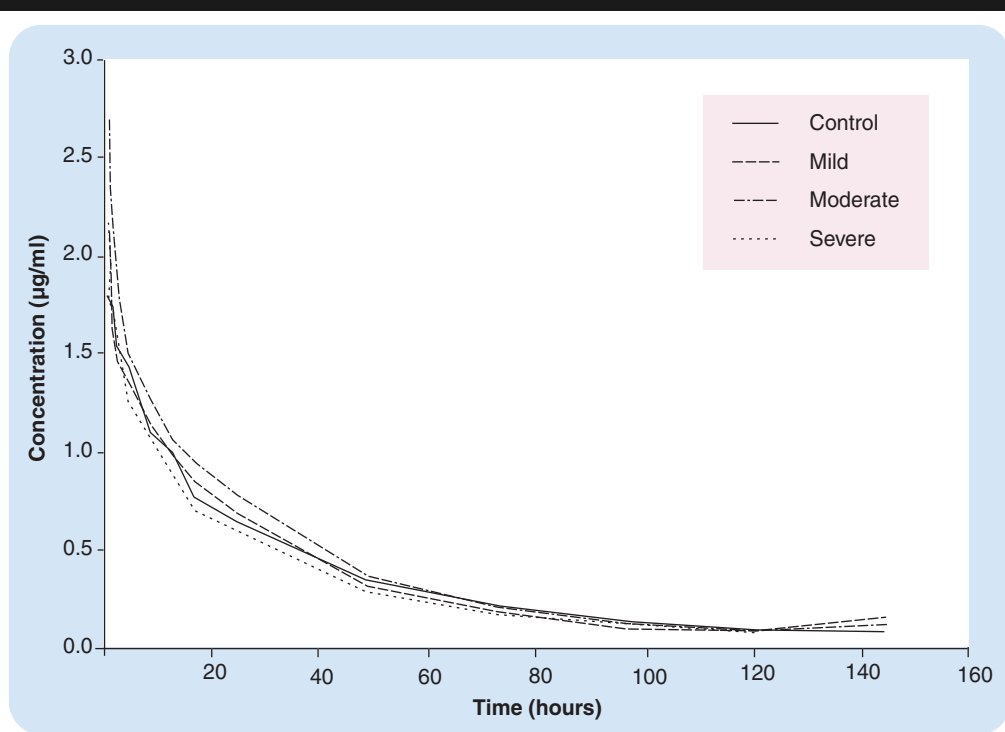
There have been several clinical trials conducted evaluating the usefulness of anidulafungin in patients suffering from EC, candidemia, IC and antifungal-refractory mucosal candidiasis (Table 4).

#### *Esophageal candidiasis*

The efficacy of anidulafungin in treating EC was studied in a randomized, double-blind, controlled clinical trial that included

601 patients with endoscopically proven EC [66]. A total of 300 patients received a loading dose of 100 mg anidulafungin intravenously, followed by anidulafungin 50 mg/day, while 301 patients received oral fluconazole 100 mg/day. Treatment was continued for 14 to 21 days (a minimum of 7 days after resolution of symptoms). Of the 504 patients who completed therapy, 242 of 249 (97.2%) who received anidulafungin and 252 of 255 (98.8%) who received fluconazole showed endoscopic evidence of cure or improvement (treatment difference: -1.6%; 95% confidence interval [CI], -4.1–0.8), indicating that anidulafungin is at least as efficacious as fluconazole in the treatment of EC. Mycologic cure rates were also similar, with 86.7% efficacy for anidulafungin and 90.9% for fluconazole. The one difference between the two treatment arms was the relapse rate at the 2-week follow-up. The relapse rates were 35.6% with anidulafungin and 10.5% with fluconazole ( $p < 0.001$ ). The rate with caspofungin was 26%, which was slightly lower than that of anidulafungin [67]. The cause of this greater relapse rate by echinocandins compared with fluconazole is unknown. It may be due to lower levels of echinocandins in the tips of the villi, thus producing lower mycologic eradication rates, which may eventually lead to higher relapse rates (Table 4).

**Figure 4. Serum anidulafungin concentrations in patients with mild, moderate and severe renal impairment, compared with controls.**



Adapted from [50].

#### ***Azole-refractory mucosal candidiasis***

Due to its candidacidal activity, anidulafungin may be effective in managing patients with fluconazole-refractory mucosal candidiasis. An open-label clinical trial evaluated adults with signs and symptoms of either OPC or EC and endoscopic and microbiologic documentation of disease after at least 14 days of fluconazole treatment (>200 mg/day) [68,69]. Of the 19 patients enrolled in the study, 17 had a diagnosis of AIDS (CD4 cell count: <50 cells/mm<sup>3</sup> and azole-refractory OPC or EC). One patient had recurrent OPC due to xerostomia and one patient was diagnosed with mucocutaneous candidiasis. *C. albicans* was identified in 18 patients at baseline; five patients had mixed infections with *C. albicans* and *C. glabrata*, while 11 patients had documented fluconazole nonsusceptible *Candida* isolates. At the end of the study, 18 patients had a successful clinical response, and 11 of 12 patients with EC were considered endoscopic successes (cure or improvement). Although the study was small and open-label, the data suggest that anidulafungin was clinically effective and well-tolerated in those patients with azole-refractory mucosal candidiasis. In addition, anidulafungin was well tolerated, with only one serious adverse event (rash).

Overall, anidulafungin may offer an additional treatment option in patients suffering from azole-refractory mucosal candidiasis, a disease associated with high morbidity and occasional mortality (Table 4).

#### ***Invasive candidiasis***

A Phase II, open-label, dose-ranging study was conducted in 123 patients with candidemia and signs or symptoms of active infection [48]. Participants received anidulafungin at 50, 75 or 100 mg/day and were followed up for a maximum of 42 days. Baseline *Candida* spp. (n = 127 isolates) were obtained from 116 patients. The species distribution included *C. albicans* 53%, *C. glabrata* 31%, *C. parapsilosis* 9%, *C. tropicalis* 9% and *C. krusei* 4%. Therapy was successful (defined as cure or improvement) in 73 of 83 patients who completed the study (84, 90 and 89% with 50, 75 and 100 mg/day doses, respectively). The response rates of the patients defined as cured (68 of 83 patients) were 72, 85 and 83%, at the respective three doses. The five remaining patients were considered improved by definition; however, they still required more than 2 weeks of antifungal therapy. Both groups showed an apparent dose-dependent relationship



**Table 4. Anidulafungin clinical efficacy trials.**

Disease state	No. patients enrolled	Anidulafungin dose	Comparator	Efficacy	Adverse events	Ref.
Esophageal candidiasis	36	50 mg (loading), followed by 25 mg daily Or 70 mg (loading), followed by 50 mg daily	None	Endoscopic response rates: 81% (50 mg/25 mg) 85% (70 mg/50 mg)	NA	[78]
Esophageal candidiasis	601	100 mg (loading), followed by 50 mg daily	Fluconazole 200 mg (loading), followed by 100 mg daily	Endoscopic response rates: Afgn: 242/249 (97%) Flz: 252/255 (98.8%)	Afgn 9.3% Flz 12%	[66]
Candidemia and invasive candidiasis	123	Randomized to 3 doses: 50 mg daily 75 mg daily 100 mg daily	None	Global response rate (clinical and microbiologic success): 50 mg dose: 72% 75 mg dose: 85% 100 mg dose: 83%	<5% in all three groups	[48]
Candidemia and invasive candidiasis	245	100 mg daily	Fluconazole 400 mg daily	Global response rate (clinical and microbiologic success-MITT) Afgn: 75.6% Flz: 60.2%	Comparable in both arms	[71]
Antifungal refractory mucosal candidiasis	17	100 mg daily intravenously	None	18 patients clinical success 11 of 12 endoscopic success	NA	[69]

Afgn: Anidulafungin; Flz: Fluconazole; MITT: Modified intent-to-treat population; NA: Not available.

toward cure, although this was not statistically significant with the higher doses (75 and 100 mg/day). All species of *Candida* responded adequately to anidulafungin, including the non-*albicans* species *C. glabrata* and *C. parapsilosis*, for which anidulafungin MIC values tend to be higher [70]. During the follow-up period, the success rates in these very ill patients (25% had Acute Physiology And Chronic Health Evaluation [APACHEII] scores >20) were 72, 85 and 83% with the 50, 75 and 100 mg/day doses, respectively. In addition, anidulafungin was well tolerated at all doses. The few adverse events that were possibly treatment related were not considered dose related and were reported by less than 5% of patients in each dose group, with the exception of hypokalemia (reported by 10% of patients in the group receiving the lowest dose).

In a recently completed Phase III, multicenter, double-blind, randomized clinical trial, a 100 mg dose of anidulafungin was compared to a 400 mg dose of fluconazole in patients with candidemia and or IC [71]. A total of 250 subjects were enrolled in this pivotal clinical trial that showed a

global response of 76% in those patients receiving anidulafungin and 60% in those patients receiving fluconazole at the end of the treatment period (95% CI: 3.85–26.99). At the 2-week follow-up period, the response rate was 65 and 49%, respectively (95% CI: 3.14–27.68) and 56 and 44%, respectively, at the 6-week follow-up (95% CI: -0.6–24.28) [71]. Overall, the adverse event profile and the drug tolerability was similar between the two treatment groups. This is the first time a clinical trial evaluating two antifungal agents for the treatment of candidemia has been able to demonstrate the superiority of anidulafungin over its comparator, fluconazole [71].

#### Adverse event profiles

In general, adverse events have been shown to be uncommon in patients who receive anidulafungin (Table 5). An extensive review of the integrated safety databases for the four anidulafungin Phase II/III clinical studies in patients with either mucosal or IC, candidemia or aspergillosis showed a low rate of adverse events [72]. Of the 6712 doses of anidulafungin

**Table 5. Incidence of drug-related adverse events occurring in less than 1% of patients with esophageal candidiasis infection.**

<b>Adverse event</b>	<b>Anidulafungin (n = 300) (%)</b>	<b>Fluconazole (n = 301) (%)</b>
<b>Vascular disorders</b>		
Phlebitis/thrombophlebitis	4 (1.3)	4 (1.3)
<b>Blood and lymphatic disorders</b>		
Leukopenia	2 (0.7)	4 (1.3)
Neutropenia	3 (1.0)	0 (0.0)
<b>Nervous system</b>		
Headache	4 (1.3)	3 (1.0)
<b>Digestive system</b>		
Nausea	3 (1.0)	3 (1.0)
Vomiting	2 (0.7)	3 (1.0)
Dyspepsia (aggravated)	1 (0.3)	3 (1.0)
<b>General disorders</b>		
Pyrexia	2 (0.7)	3 (1.0)
<b>Total</b>	<b>4 (9.3)</b>	<b>36 (12.0)</b>

Adapted from [66].

administered, 14 plausible infusion-related adverse events were identified in six of 456 patients (1.3%) with candidiasis and three of 17 patients (17.6%) with aspergillosis. Although uncommon, the most frequent infusion-related adverse event was hypotension (0.8% in patients with candidemia/candidiasis). Anaphylaxis was not reported in any patient [73]. During the Phase I dose-ranging study that enrolled 30 subjects, infusion-related reactions (dyspnea, nausea, flushing, dizziness) occurred in one subject who received the highest dose (130 mg/day) of anidulafungin [73]. All manifestations of the infusion-related reaction resolved within 6 min of onset.

In the Phase III clinical trial comparing anidulafungin (50 mg/day) with fluconazole (100 mg/day) in 601 patients with EC, adverse events occurred at similar rates in both treatment groups (Table 5) [66]. The majority of adverse events were related to the underlying disease state (HIV/AIDS and malnutrition). The serious treatment-related adverse events were rare (two in each treatment arm). More patients receiving fluconazole (12.0%) than anidulafungin (9.3%) experienced at least one treatment-related adverse event. Treatment-related adverse events that occurred in 1% or more of patients in either treatment group are shown in Table 5. Biochemical adverse events were extremely infrequent and included increases in levels of  $\gamma$ -glutamyltransferase (1.3% of patients in each treatment group), AST (0.3% of anidulafungin-treated

patients vs 2.3% of fluconazole-treated patients) and ALT (0% anidulafungin-treated patients vs 1.0% fluconazole-treated patients). In addition, evaluation of the impact of anidulafungin on the QT interval showed no significant change from baseline measurements. Overall, none of the treatment-related events occurred in 2% or more of patients receiving anidulafungin [74].

In a Phase II dose-ranging study evaluating the efficacy and tolerability of anidulafungin in 123 patients with candidemia, two or less patients (5%) in each of the three dose groups (50, 75 and 100 mg/day) had treatment-related adverse events, with the exception of hypokalemia, which was reported in four patients (10%) receiving the 50 mg/day dose [48,70]. The only serious adverse events reported as related or possibly related to therapy were a nonfatal, non-neutropenic fever (onset on day 11) and seizure activity in two patients, both of whom had numerous complicated comorbid conditions. The different study groups showed no significant difference in hepatic function tests [70,75]. Overall, anidulafungin at doses of 50 to 100 mg/day was well tolerated and should prove useful in seriously ill patients with multiple underlying comorbid conditions.

#### Pharmacokinetic/pharmacodynamic correlations for anidulafungin

Anidulafungin has shown clinical efficacy in a broad spectrum of fungal infections in studies involving patients with EC, IC or candidemia.

By examining baseline plasma concentration data, a relationship between clinical response and pharmacokinetic properties can be observed [47]. Serum concentrations are generally maintained at greater than 1 mg/l throughout the dosing period and remain greater than 2 mg/l for more than 50% of the dosing period. Pharmacokinetic parameters demonstrate a sigmoidal-curve, dose-efficacy or concentration-dependent response in which efficacy in EC was predicted by a baseline AUC of 35 mg/l/h, steady-state clearance rate of 1.5 ml/min and clearance at  $C_{\min}$  of 1 ml/min. The recommended 50 mg/day dose of anidulafungin produces levels that exceed the drug exposure required for successful clinical response [47,76].

### Dosage & administration

Anidulafungin is administered once daily at an infusion rate not to exceed 1.1 mg/min. In treating EC, the recommended initial (loading) dose of anidulafungin is twice the daily dose of 50 mg/day [47,76]. When anidulafungin is used in the management of EC in patients with HIV infection, consideration may be given to continuing suppressive therapy after a standard course of treatment, due to the high rate of relapse in this immunocompromised population [66].

A Phase II, dose-ranging study of anidulafungin in patients with IC/candidemia showed high success rates with 75 and 100 mg/day doses at the end of therapy (90 and 89%, respectively) and at follow-up (85 and 83%, respectively), suggesting the use of 100 mg/day anidulafungin for treating candidemia and IC [48]. A Phase III, double-blind, randomized clinical trial that was recently completed to evaluate the efficacy and tolerability of anidulafungin 100 mg/day in candidemia and IC verified the efficacy of the 100 mg dose of anidulafungin [71].

### Expert commentary

Anidulafungin appears to have several advantages over other antifungal medications. The efficacy and safety profile of anidulafungin, plus its unique pharmacokinetic characteristics, make it a suitable alternative antifungal compound for first-line therapy of mucocutaneous candidiasis, candidemia, systemic candidiasis and antifungal-refractory mucosal candidiasis. Anidulafungin provides a broad spectrum of activity with proven efficacy against a wide array of *Candida* spp., including those that are azole or polyene resistant. In addition, anidulafungin also has potent *in vitro* and *in vivo* activity

against *Aspergillus* spp. Another advantage of anidulafungin is that dosing adjustments are not necessary for patients based on age, sex, body weight, disease state, concomitant drug therapy, or renal or hepatic insufficiency. Furthermore, the mechanism of action for anidulafungin does not appear to induce cross-resistance with other classes of antifungals [20,21]. Based on a lack of interaction with amphotericin B and voriconazole, anidulafungin is well suited for use in combination with other antifungal agents [39,64].

### Role of anidulafungin in the antifungal armamentarium

Since anidulafungin is in late Phase III development, some of the data are still being evaluated. However, it is known that its documented *in vitro* and *in vivo* efficacy, together with its safety profile, may facilitate the use of anidulafungin in future management of serious fungal infections beyond that of mucosal candidiasis. Results of recently completed clinical trials will eventually determine the role of anidulafungin in the management of mucosal and invasive fungal infections.

### Prophylaxis

The use of anidulafungin as primary prophylaxis may be a viable addition to the treatment armamentarium in patients undergoing solid-organ or stem-cell transplantation, those with AIDS and those with refractory fungal EC infections who are prone to recurrences [77]. In addition, anidulafungin may prove useful as an empiric antifungal agent for the management of high-risk patients in intensive care units who may require empiric antifungal therapy despite negative blood cultures.

### Candidemia & invasive candidiasis

Anidulafungin may be beneficial in the treatment of candidemia and IC [71]. Open-label studies have shown success rates between 84 and 90% in patients with documented candidemia [48]. The overall safety profile of anidulafungin, along with the lack of hepatotoxicity and minimal drug–drug interactions, offers an advantage over the currently recommended treatment of invasive fungal infections [16,77]. In addition, preliminary data from the recently completed pivotal Phase III trial comparing anidulafungin with fluconazole also shows great promise in treating candidemia and candidiasis in this difficult patient population [71].

### *Invasive aspergillosis*

*In vitro* studies have shown significant activity of anidulafungin against *Aspergillus* spp. [44]. Clinical trials are underway to evaluate the efficacy and tolerability of anidulafungin in invasive aspergillosis. In addition, anidulafungin appears to be well tolerated when administered concomitantly with other antifungals, such as voriconazole and LAMB. In a small, open-label clinical trial, patients with invasive aspergillosis received anidulafungin (100 mg/day) alone or in combination with LAMB. No significant differences in the pharmacokinetic profile of anidulafungin were demonstrated between the two treatment groups [56]. Furthermore, anidulafungin has shown synergistic or additive activity *in vitro* against aspergilli when given in combination with either voriconazole or amphotericin B [39,40].

### *Pediatric use*

Mucosal and invasive fungal infections are a serious dilemma in premature infants, children with hematologic malignancies and HIV-infected children [77]. Compared with currently recommended antifungal agents (amphotericin and fluconazole), anidulafungin has shown efficacy and tolerability in candidiasis, which merits its consideration for use in this high-risk group.

### *Azole-refractory pathogens*

Anidulafungin has been shown to be effective in treating azole-refractory mucosal fungal infections in HIV-infected patients, with a 100% clinical success rate by the end of treatment [68,69]. The results of this noncomparative study suggest the potential utility of anidulafungin as an induction therapy for this difficult-to-treat population and possibly as secondary prophylaxis in patients at high risk of recurrence [68,69].

### *Outlook*

The incidence of serious fungal infections has increased dramatically over the past 25 years and continues to do so. It is known that some fungal species are intrinsically resistant to polyenes or azoles and that several species of *Candida* and *Aspergillus* can develop secondary resistance to conventional antifungal therapy. Furthermore, the epidemiology of invasive fungal infections has changed substantially over the past decade. Although *Candida* spp. are still the most common cause of fungal infections among

all compromised hosts, in many institutions that care for transplant recipients or patients with hematologic malignancies, systemic infections due to *Aspergillus*, *Fusarium* and *Zygomycetes* have become the major cause of morbidity and mortality, affecting as many as 30% of patients. The major dilemma concerning these emerging mold infections is the fact that few conventional antifungals have demonstrated activity against them.

In addition to the shift in fungal genera observed in these severely compromised patients, there has also been a recent significant shift in the distribution of *Candida* spp. producing systemic infections. Although *C. albicans* remains the primary cause of candidial infection, it only comprises approximately 45% of *Candida* isolates recovered from hospitalized patients. In a recent study, the incidence of non-*albicans Candida* spp. demonstrated a dramatic increase in frequency, especially due to *C. glabrata*, *C. parapsilosis* and *C. tropicalis*, all of which are generally less susceptible to conventional antifungal agents.

The recent fungal shifts to the more resistant fungal genera (*Aspergillus*, *Fusarium*, *Zygomycetes*) and to the non-*albicans Candida* spp. have certainly impacted the way clinicians manage systemic fungal infections, recognizing the urgent need for newer antifungals with broader spectrums of activity and improved adverse event profiles.

In addition, due to these emerging fungi and the advent of newer antifungal agents such as voriconazole, posaconazole, caspofungin, micafungin and now anidulafungin, many clinicians have begun to use combination antifungal therapy for the more difficult-to-treat mold infections found in these severely immunocompromised hosts. The most frequently used combination appears to be voriconazole and caspofungin, followed by caspofungin and amphotericin B. These combinations have demonstrated *in vitro* additive or synergistic activity against many of the more resistant fungi. Despite the lack of clinical trials, but due to the theoretically improved activity and spectrum of activity using combination antifungal therapy, the future of antifungal therapy appears to be heading in the direction of combination antifungals as a standard of care. This appears especially true in severely immunocompromised patients with mold infections such as invasive aspergillosis or disseminated zygomycosis.

### Conclusions

With its spectrum of activity, clinical efficacy and safety profile, anidulafungin appears to be an attractive addition to the current antifungal armamentarium. Study results thus far warrant further clinical trials evaluating the use of anidulafungin as either primary or preemptive therapy for invasive fungal infections, such as candidiasis and aspergillosis. Due to an apparent lack of adverse drug interactions associated with anidulafungin and the *in vitro* additive or synergistic activity when it is administered concomitantly with other antifungals (i.e., conventional amphotericin B, LAMB or voriconazole), this drug should be further explored in the management of some of the more deadly mold infections, such as aspergillosis. Anidulafungin also

shows potential in the management of azole refractory OPC and EC, which frequently prove difficult-to-manage and are associated with a high incidence of morbidity and early mortality in the HIV-infected population.

Although data from clinical trials are currently limited, anidulafungin has shown promising *in vitro* and clinical activity, a unique pharmacokinetic profile and a favorable tolerability profile. Completed clinical studies suggest that anidulafungin may be useful for treating a range of serious fungal infections, including mucocutaneous candidiasis, candidemia, IC, azole-refractory mucosal candidiasis and possibly invasive aspergillosis, either as monotherapy or as part of a combination-therapy regimen.

### Highlights

- Anidulafungin is a novel antifungal in the family of the echinocandins.
- The mechanism of action involves the noncompetitive inhibition of  $\beta$ -1,3-D-glucan synthase, resulting in the selective inhibition of the synthesis of glucan. Glucan, a major structural component of the cell wall of many pathogenic fungi, is not present in mammalian cells, therefore offering a selective target for the echinocandins antifungals.
- Anidulafungin provides a broad spectrum of activity with proven efficacy against a wide array of *Candida* and *Aspergillus* spp., including those strains that are azole or polyene resistant.
- An important advantage of anidulafungin is that dosing adjustments are not necessary for patients based on age, sex, body weight, disease state, concomitant drug therapy, or renal or hepatic insufficiency.
- Based on a lack of interaction with amphotericin B and voriconazole, anidulafungin is well suited to be used in combination with other antifungal agents.
- The efficacy and safety profile of anidulafungin, plus its unique pharmacokinetic characteristics, make it a suitable alternative antifungal compound for first-line therapy of mucosal candidiasis, candidemia, systemic candidiasis and antifungal-refractory mucosal candidiasis.

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