Anidulafungin: a new addition to the antifungal armamentarium

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Invasive fungal infections continue to be associated with high rates of morbidity and mortality, primarily in the immunocompromised hosts. *Candida* and *Aspergillus* are the most common causes of invasive fungal disease; however, other fungi can also cause disease in humans. Current therapeutic options for the management of invasive fungal infections include the polyenes, triazoles and echinocandins. Anidulafungin is a new echinocandin antifungal drug with a favorable toxicity profile and minimal drug–drug interactions that has activity against *Aspergillus* and *Candida*, including azole-resistant strains.

Despite large advances in the development of antifungal drugs, invasive fungal infections continue to contribute greatly to the overall morbidity and mortality in immunocompromised patients [1]. *Candida* has been associated with a wide spectrum of disease, ranging from catheter-associated infections to disseminated, deep organ disease [2]. While hematological malignancies and solid organ transplants are well established risk factors for fungal infections, prolonged stay in the intensive care unit, the presence of central venous catheters, prolonged broad spectrum antibiotics, parenteral nutrition, recent surgery (particularly intra-abdominal surgery), diabetes, hemodialysis and pancreatitis have also been identified as risk factors for invasive candidiasis [3]. Oropharyngeal/esophageal candidiasis is the most common opportunistic infection in patients with HIV, occurring in one in five infected patients. In addition, *Candida* has become the fourth most common cause of nosocomial-bloodstream infections with an attributable mortality as high as 40% [1,4].

Aspergillus is ubiquitous mold found in the environment capable of causing invasive fungal infections in nearly every organ in the immunocompromised host. However, the pulmonary system is most commonly affected [5]. The incidence of invasive aspergillosis varies by the underlying host factors; however, it can occur in as many as 25% of patients with acute leukemia or undergoing lung transplantation [5]. In patients undergoing hematopoetic stem cell transplantation (HSCT), especially those who develop Graft-versus-host disease, *Aspergillus* has emerged as a problem pathogen. The overall mortality rate of patients with invasive aspergillosis is 60%; however, in patients undergoing bone marrow transplant or in those patients with cerebral involvement, the case fatality rate increases to nearly 90% [6].

With the widespread use of azoles in the management and prevention of fungal infections, there has been a shift towards an increase of non-*albicans Candida* species, primarily *Candida glabrata,* which has reduced susceptibility to the azoles [7]. In addition, the use of azoles in prophylaxis of fungal infections in high-risk patients has shifted the epidemiology towards invasive molds, such as *Aspergillus.* Newer antifungal agents with activity against a broad spectrum of fungi and favorable safety profiles are needed. Anidulafungin (Eraxis®, Pfizer Inc., NY, USA) is the newest addition to the antifungal armamentarium, which has a broad spectrum of activity to include *Aspergillus* and *Candida* species (including fluconazole-resistant strains) and a favorable safety and drug–drug interaction profile.

Overview of the antifungal market

There have been a large number of new antifungal drugs that have emerged since fluconazole was US FDA approved in 1990. Currently, there are four FDA-approved triazole antifungals available in the USA: fluconazole (Diflucan®, Pfizer Inc., NY, USA), itraconazole (Sporonox®, Ortho Biotech, NJ, USA), voriconazole (Vfend®, Pfizer, Inc., NY, USA) and posaconazole (Noxafil®, Schering-Plough, NJ, USA). Generally speaking, fluconazole has the narrowest spectrum of activity, followed by itraconazole and voriconazole, which increase in spectrum to include *Aspergillus*, and finally posaconazole, which has the activity of itraconazole and voriconazole with the additional spectrum to include the Zygomycetes, such as *Rhizopus* and *Mucor*.

Keywords: anidulafungin, *Aspergillus*, *Candida*, echinocandins

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In addition to the triazoles, polyenes have also been used to manage invasive fungal infections. The polyenes include amphotericin B and the lipid formulations amphotericin B lipid complex (ABLC; Abelcet®, Enzon, NJ, USA), amphotericin B colloidal dispersion (ABCD; Amphotec®, Three Rivers Pharmaceuticals, PA, USA) and liposomal amphotericin B (LAmB; Ambisome®, Astellas Pharma US, Inc., IL, USA). The polyenes are the broadest spectrum fungicidal compounds available in the antifungal armamentarium; however, any pharmacological advantage of amphotericin B is overshadowed by the high rates of nephrotoxicity and infusion-related reactions. Although the lipid formulations have a lower rate of nephrotoxicity than the deoxycholate formulation, the lipid formulations still have higher rates of nephrotoxicity when compared with the azoles or the echinocandins [8,9].

The echinocandins are the most recent class of drugs to be added to the antifungal armamentarium. Caspofungin acetate (MK991, Cancidas®, Merck & Co., Inc, NJ, USA), micafungin sodium (FK463, Mycamine®, Astellas Pharma US, Inc., IL, USA) and anidulafungin (LY303366, VER002, Eraxis®, Pfizer Inc.) are the three currently FDA-approved echinocandins available in the USA. All three agents have similar spectrums of activity and toxicity profiles; however, they have slightly different pharmacokinetic profiles. Anidulafungin received FDA approval on February 21, 2006, for the treatment of esophageal candidiasis and candidemia with other forms of *Candida* infections, including intra-abdominal abscess and peritonitis.

Introduction to anidulafungin

Chemistry

Anidulafungin is a semisynthetic lipopeptide synthesized from a fermentation byproduct of *Aspergillus nidulans* (**Figure 1**). Unlike the polyenes and azoles, which exert their antifungal activity on the fungal cell membrane, anidulafungin acts by inhibiting the formation of (1,3)-β-D-glucan, an integral component of the fungal cell wall. The inability of the fungi to cross link (1,3)-β-D-glucan and (1,6)-β-D-glucan results in loss of structural integrity of the cell wall, resulting in rapid fungicidal activity against *Candida* and fungistatic activity against *Aspergillus* [10]. The selective effects on the cell wall rather than the cell membrane of the fungi are advantageous to the echinocandin class. Since eukaryotic cells do not have cell walls, the direct cellular toxicity seen with the polyenes is absent with the echinocandins. In addition, organisms that are resistant to the polyenes and azoles may be susceptible to the echinocandins.

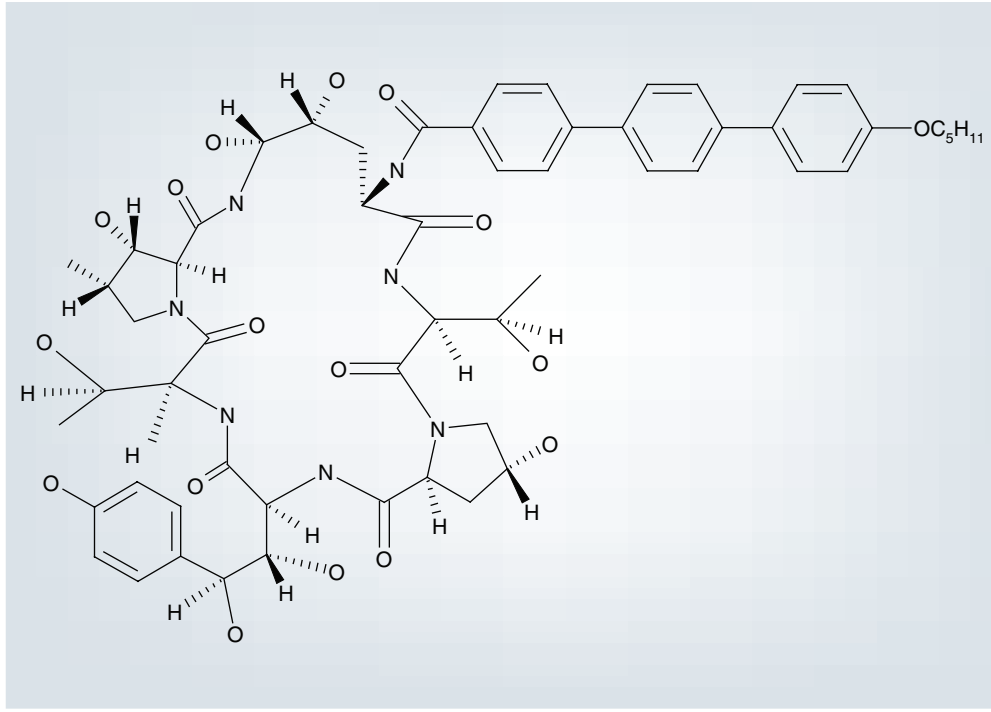
Microbiology

Interpretive breakpoints for anidulafungin have not been established by the Clinical and Laboratory Standard Institute (CLSI). The *in vitro* activity of the anidulafungin may be related to the β-glucan content of the organism [11]. Anidulafungin has potent *in vitro* activity against *Candida albicans, C. glabrata, Candida tropicallis* and *Candida krusei* as well as *Aspergillus fumigatus.* Although anidulafungin maintains potent *in vitro* activity against strains of *C. glabrata* that have elevated minimum inhibitory concentrations (MICs) to caspofungin, the clinical significance of this finding is unknown [12]. The MIC_{50} and MIC_{90} for *Candida parapsilosis* is 2 and 4 μg/ml, respectively [13]. The higher MIC's with *C. parapsilosis* is consistent with what is observed with caspofungin and micafungin, and the clinical relevance is not known [14,15]. In addition, anidulafungin does not demonstrate *in vitro* activity against *Cryptococcus neoformans*, *Fusarium* spp., *Rhizopus* spp. or *Mucor* spp. [16]. Anidulafungin demonstrates variable activity against *Blastomyces dermatitidis* and *Hisptospasma capsulatum* with MICs of 2–8 and 2–4 μg/ml, respectively [17].

Pharmacokinetics

A summary of the pharmacokinetic properties of anidulafungin is presented in **Table 1**. Anidulafungin is only available as a parenteral product. Upon intravenous injection, it is rapidly taken up into the tissues after administration and then slowly eliminated with a half-life of approximately 24 h [18,19]. The overall volume of distribution of anidulafungin is between 30 and 50 l, which is similar to total body fluid volume. Unlike micafungin and caspofungin, anidulafungin is not metabolized by the liver. Instead, anidulafungin undergoes slow chemical degradation into a chemically inactive peptide whereby the cleaved ring products are further broken down into peptidic degradants and eliminated [18]. The majority of the excreted anidulafungin is through the feces, with 10% excreted as intact drug and less than 1% of the dosage eliminated in the urine. The average dose for anidulafungin is 50–100 mg/day after a 100–200 mg loading dose, depending on the indication. Dosage

Figure 1. Anidulafungin.



adjustments of anidulafungin are not recommended in patients with hepatic insufficiency, renal insufficiency or hemodialysis.

The pharmacokinetics of anidulafungin have been evaluated in children with neutropenia [20]. Patients aged 2–17 years were divided into two cohorts of patients (2–11 and 11–17 years) and received anidulafungin 0.75 or 1.5 mg/kg/day for at least 5 days. Anidulafungin pharmacokinetics were similar between the two cohorts within each dosage group. Drug exposure correlated more with body weight than age. Anidulafungin 0.75 and 1.5 mg/kg/day in children provided exposures that were achieved with 50 and 100 mg/day in adults with invasive fungal disease [17].

Table 1. Pharmacokinetic parameters of anidulafungin in healthy adults.

Parameter	Value
$C_{max,ss}$ (mg/l)	8.6*
AUC_{ss} (mg*h/l)	112*
Vd (l)	30–50
Protein binding	85–90%
Hepatic metabolism	None. Chemically degraded with 30% eliminated in the feces
Renal excretion	<1%
Half-life (h)	24
Clearance (l/h)	0.8–1.0

**200 mg loading dose, followed by 100 mg/day for 10 days.*
AUC_{ss}: Steady state area under the plasma concentration curve; $C_{max,ss}$: Steady state maximum concentration in plasma; Vd: Volume of distribution.

Animal studies

Anidulafungin has shown excellent *in vivo* activity in a variety of animal models. Two recent studies on models of *C. glabrata* and *Aspergillus fumigatus* are discussed below as examples of the activity seen. The efficacies of fluconazole, amphotericin B and anidulafungin were evaluated in a neutropenic murine model of disseminated candidiasis with three different strains of *C. glabrata* [21]. Mice were inoculated via the lateral tail vein and sacrificed over a 96-h period where the kidneys were harvested for determination of fungal burden and drug concentrations. While amphotericin B produced a 4.12 log reduction at 24 h for the strain with an amphotericin B MIC of 0.25 µg/ml, there was no effect on the strain that had an MIC of 2 µg/ml. Fluconazole produced a 1.33 log reduction for the fluconazole-susceptible strain, however, it did not have an effect on the susceptible dose-dependent nor -resistant strain. Anidulafungin produced a 1.38–1.87 log reduction in kidney

fungal burden and this effect was not dependent on fluconazole or amphotericin B activity. In addition, there was a persistent fungal decline at 96 h after a single dose of anidulafungin in this model, demonstrating excellent *in vitro* activity against *C. glabrata*.

Anidulafungin and amphotericin B were evaluated against amphotericin B-susceptible and -resistant strains of *Aspergillus fumigatus* in a neutropenic murine model of invasive aspergillosis [22]. Mice were inoculated via the lateral tail vein and monitored for survival over 11 days. At day 11, surviving mice were sacrificed, and their lungs and kidney's were removed, homogenized and plated for colony counts. Anidulafungin produced a survival benefit and a greater reduction in tissue colony counts compared with amphotericin B. This effect was dose dependent and was greater with the amphotericin-susceptible strain. Nonetheless, anidulafungin was shown to be effective against *Aspergillus fumigatus* in a murine model of invasive aspergillosis and this warrants future human clinical trials.

Clinical efficacy

Esophageal candidiasis

Anidulafungin 100 mg loading dose followed by 50 mg/day has been compared with fluconazole 200 mg loading dose, followed by 100 mg/day maintenance dose in a randomized, double-blind clinical trial in 601, predominantly HIV-positive, patients with esophageal candidiasis [23]. Endoscopic resolution of lesions after 14–21 days of treatment was determined and was graded as either cured (complete resolution of lesions) or improved. In addition, clinical response, defined as an absence or improvement in symptoms compared with baseline, was determined. Endoscopic cure or improvement at the end of treatment was present in 97.2 and 98.8% of anidulafungin- and fluconazole-treated patients, respectively, and clinical response occurred in 98.8 and 99.6% of anidulafungin- and fluconazole-treated patients, respectively. However, at the 2-week follow-up, only 64.4% of the anidulafungin-treated patients had a sustained endoscopic success compared with 89.5% of fluconazole-treated patients ($p < 0.001$). However, patients' immune status was not controlled for and more patients in the fluconazole group received antiretroviral drugs for their HIV compared with the anidulafungin group, potentially explaining the lack of sustained response with anidulafungin.

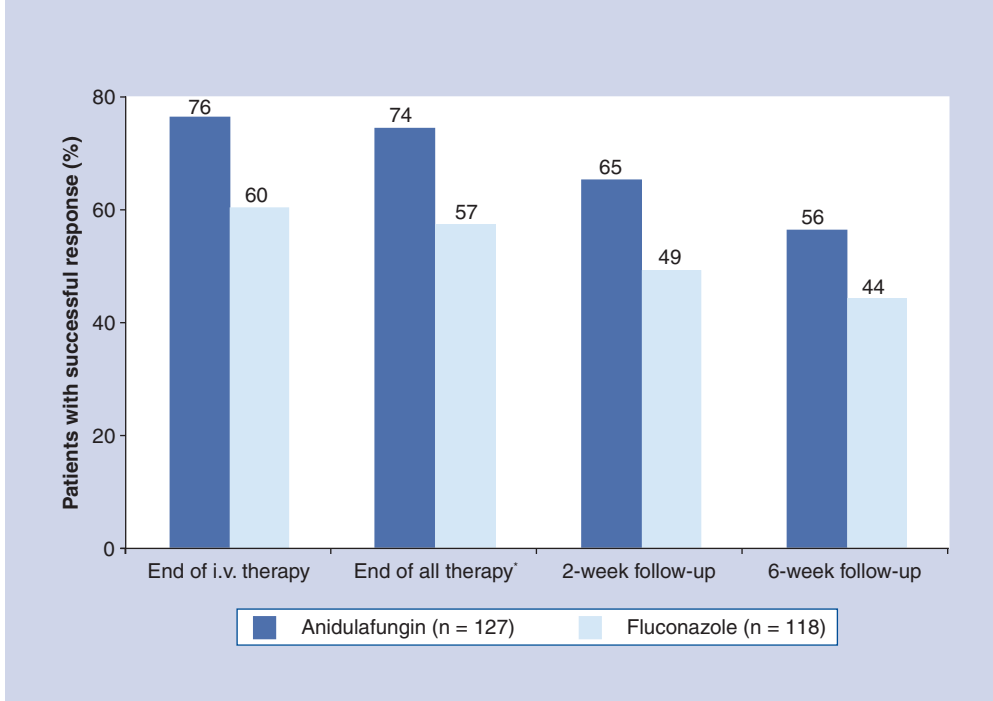
Candidemia

In an open-label evaluation of anidulafungin predominantly in patients with candidemia (6% of patients had invasive candidiasis without evidence of candidemia), there was an 84, 90 and 89% overall clinical success rate at the end of treatment with 50, 75 and 100 mg/day, respectively [24]. In a pivotal, Phase III, randomized (1:1), double-blind study of candidemia and invasive candidiasis, anidulafungin 200 mg loading dose, followed by 100 mg/day was compared with fluconazole 800 mg loading dose, followed by 400 mg/day for 14 days from the last positive blood culture [18,25]. This study was conducted at over 60 centers in the USA, Canada and Europe. Patients in both study arms were permitted to step down to oral fluconazole after they received 10 days of intravenous therapy, if clinically indicated. Patients included in this study were largely non-neutropenic (97%), with 80% of the patients having Acute Physiology and Chronic Health (APACHE II) scores less than 20 and the most common pathogen isolated at baseline was *Candida albicans*. At the end of intravenous therapy, there was a 75.6% overall clinical response with anidulafungin compared with a 60.2% response with fluconazole. (Difference = 15.4%; 95% CI: 3.9–27.0; $p = 0.01$) (**Figure 2**). This improved difference in efficacy with anidulafungin was maintained at 2 weeks after the end of treatment. The overall mortality at 6 weeks after the end of treatment was higher in the fluconazole-treated patients compared with anidulafungin (33 vs 23%), however, this was not statistically significant.

Drug interactions

Since anidulafungin is not a substrate for, inhibitor of, or inducer of the cytochrome P450 isoenzyme system, it would not be expected to interact with drugs metabolized by these systems. In a study of 12 healthy adults receiving anidulafungin 100 mg/day for 8 days after an initial loading dose of 200 mg, coadministration with cyclosporine 1.25 mg/kg twice daily did not result in a change in C_{max} of anidulafungin or cyclosporine [26]. The $AUC_{0–24}$ of anidulafungin was increased by 22%, which was considered clinically insignificant and the overall exposure of cyclosporine was not affected. In a study of 17 healthy adults receiving concomitant anidulafungin and voriconazole, the C_{max} and AUC of both anidulafungin and voriconazole were not significantly altered with the

Figure 2. Anidulafungin versus fluconazole for the treatment of candidemia in the modified intent-to-treat population.



*33 patients in each arm converted to oral fluconazole after at least 10 days of intravenous (i.v.) treatment.
End of i.v. therapy: treatment difference: 15.4; 95% CI: 3.9–27.0.
End of all therapy: treatment difference: 17.2; 95% CI: 2.9–31.6.
2-week follow-up: treatment difference: 15.4; 95% CI: 0.4–30.4.
6-week follow-up: treatment difference: 11.8; 95% CI: -3.4–27.0.

co-administration [27]. In three additional pharmacokinetic drug-interaction studies, anidulafungin was coadministered with tacrolimus, LAmB and rifampin [19]. The coadministration of anidulafungin with each of these compounds also did not demonstrate any changes of C_{max} or AUC. Overall, the very favorable drug interaction and pharmacokinetic profile of anidulafungin make it an attractive agent for the treatment of invasive fungal infections, especially in the complex patient receiving concomitant cytochrome P450 inhibitors, inducers and/or substrates.

Safety & tolerability

The most common adverse events with anidulafungin compared with fluconazole in the esophageal candidiasis and candidemia clinical trials are summarized in **Table 2**. In a Phase III clinical trial of anidulafungin compared with fluconazole for the treatment of esophageal candidiasis, 43 out of 300 (14.3%) of the patients receiving anidulafungin 50 mg/day experienced at least one treatment-emergent adverse event compared with 50 out of 301 (16.6%) of patients receiving fluconazole 100 mg/day [23]. The most common adverse events with anidulafungin were increases in γ-glutamyl transferase (1.3%), headache (1.3%), nausea (1%) and neutropenia (1%). However, these incidents were similar in patients receiving fluconazole. The number of subjects experiencing at least one adverse event in a Phase III clinical trial of anidulafungin 100 mg/day compared with fluconazole 400 mg/day for the treatment of candidemia was 32 out of 131 (24.4%) and 33 out of 125 (26.4%), respectively [18]. The most frequent adverse events were diarrhea (4/131; 3.1%), hypokalemia (4/131; 3.1%) and increased alanine aminotransferase (ALT; 3/131; 2.3%), which were no different than those seen with the comparator. There have been several reports of infusion-related toxicities, including hypotension and flushing, with anidulafungin [24]. However, the overall incidence of infusion-related reactions can be minimized by infusing anidulafungin at a rate not exceeding 1.1 mg/min [18].

Table 2. Possible or probable treatment-emergent adverse events in patients receiving anidulafungin or fluconazole for the treatment of candidemia or esophageal candidiasis.

Adverse event	Anidulafungin 100 mg/day (n = 131) [18]	Fluconazole 400 mg/day (n = 125) [18]	Anidulafungin 50 mg/day (n = 300) [23]	Fluconazole 100 mg/day (n = 301) [23]
Increased ALT	2.3%	3.2%	-	1%
Increased AST	0.8%	2.4%	0.3%	2.3%
Neutropenia			1%	
Hypokalemia	3.1%	2.4%		
Diarrhea	3.1%	1.6%		
Nausea			1%	1%
Headache			1.3%	1%
Vomiting			0.7%	1%
Deep-vein thrombosis	0.8%	2.4%		
Phlebitis/ thrombophlebitis			1.3%	1.3%

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Expert commentary

The development of new antifungal drugs provides some light at the end of the tunnel since the overall outcomes of patients with invasive fungal infections has historically been quite poor. This may be related to the type of hosts that develop invasive fungal infections or related to suboptimal pharmacological treatments available to date. However, a critical evaluation of the evidence must be undertaken before complete integration into the clinical arena.

As a class, the echinocandins have demonstrated utility in the management of invasive fungal infections, primarily candidiasis and aspergillosis. Despite *in vitro* activity against *Aspergillus* spp. and animal models of disseminated aspergillosis, human trials with anidulafungin for aspergillosis are lacking and therefore, it cannot be recommended as a treatment option for patients at this time. However, investigations with anidulafungin alone and in combination with other drugs for invasive aspergillosis are currently being conducted [101].

Anidulafungin has demonstrated efficacy in the treatment of esophageal candidiasis at the end of therapy. However, patients treated with anidulafungin had a higher relapse rate than those treated with fluconazole [23]. The reason and clinical significance of these relapse rates are unknown and may be more related to the host immune function that to the drug.

Anidulafungin has demonstrated numerical superiority over fluconazole for the treatment of candidemia and invasive candidiasis [18,25]. However, further clinical trials are required to confirm this finding, as this was a single noninferiority trial and it was not designed to show superiority in its primary analysis. Of note is the fact that these data cannot be extrapolated to patients who are neutropenic, as less than 4% of patients in the trial had an absolute neutrophil count (ANC) less than 500 cells/mm^3.

Other clinical trials comparing echinocandins with polyenes demonstrated noninferiority with regards to clinical outcomes; however, the polyene-treated patients (both amphotericin B deoxycholate and LAmB) had a higher rate of nephrotoxicity [9,14].

A conservative conclusion, with respect to invasive candidiasis, is that the echinocandins provide the activity of the polyenes with the safety of the azoles. Currently, there is insufficient data to date to support the position that one echinocandin is superior to another for the treatment of invasive candidiasis [28]. Anidulafungin offers a safe and effective option with minimal to no concerns of drug–drug interactions.

Future perspective

A recent analysis of the treatment of invasive candidiasis demonstrates the importance of avoiding delays in therapy and that early initiation of therapy is associated with improved patient outcomes [29]. While this concept has not been demonstrated with invasive aspergillosis, intuitively, it should hold true and investigations are needed to confirm this presumption. Nonetheless, the approach of early treatment stresses the

importance of empiric or pre-emptive antifungal therapy. Empiric antifungal therapy is given to patients who are at risk for invasive fungal infections and have signs and symptoms of infection, despite treatment with appropriate antibiotics [30]. Pre-emptive therapy is similar to antifungal prophylaxis; however, the patient is at high risk, is not demonstrating any signs or symptoms of disease, and has a positive surveillance culture or has a positive test for a fungal antigen [31]. Fungal antigen tests (galactomannan and β-D-glucan) are performed on serum to provide additional evidence of an invasive fungal infection, either candidiasis or aspergillosis. These antigen tests have the potential to provide an early and rapid diagnosis, followed by early initiation of antifungal therapy, which is likely to be the key to reducing the overall mortality associated with invasive fungal infections.

The echinocandins, including anidulafungin, will probably be at the forefront of these approaches and there will undoubtedly continue to be an emergence of azole-resistant *Candida*. In addition, echinocandins, as a part of a combination regimen with either a polyene or an anti-aspergillus azole antifungal, will likely be a popular combination for the treatment of invasive aspergillosis due to the different mechanisms of action. In fact, *in vitro* studies demonstrate voriconazole or itraconazole in combination with anidulafungin are synergistic against *Aspergillus* [32].

While we can foresee the importance of early diagnosis for candidiasis and aspergillosis and the role of combination therapy for invasive aspergillosis, we should not be without concern. There will need to be continued evaluation of newer antifungal agents with novel targets in addition to continued searches for other fungal antigens, including polymerase chain reaction. This approach, in conjunction with rational antifungal use, including anidulafungin, will provide the tools to optimize the overall management of patients with invasive fungal infections.

Disclosure

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Executive summary

- Anidulafungin is a new parenteral echinocandin antifungal drug.
- Anidulafungin demonstrates *in vitro* activity against strains of *Candida* spp., including strains that are resistant to fluconazole.
- In patients with candidemia, anidulafungin was associated with a significantly higher overall success rate compared with patients treated with fluconazole.
- The pharmacokinetic profile supports single daily dosing, without dose adjustments for geriatric age, race, concomitant administration of medications that are known inhibitors/inducers/substrates of the cytochrome P450 isoenzyme system or liver and/or renal insufficiency.
- The most common adverse events associated with anidulafungin are related to the gastrointestinal system.

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• **Large, multicenter susceptibility testing survey that evaluated minimum inhibitory concentrations for multiple *Candida* species, including rarer species isolated from patients bloodstream against amphotericin B, flucytosine, fluconazole, itraconazole, voriconazole, posaconazole, caspofungin, micafungin and anidulafungin by broth microdilution.**

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