Echinocandins: The Expanding Antifungal Armamentarium

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The echinocandins are large lipopeptide molecules that, since their discovery approximately 41 years ago, have emerged as important additions to the expanding armamentarium against invasive fungal diseases. Echinocandins exert in vitro and in vivo fungicidal action against most Candida species and fungistatic action against Aspergillus species. However, the population of patients at risk for developing invasive fungal infections continues to increase. New therapeutic strategies using echinocandins are needed to improve clinical outcomes in patients with invasive fungal disease.

Keywords. echinocandin; caspofungin; anidulafungin; micafungin; invasive fungal disease.

Echinocandins are semisynthetic cyclic lipopeptides that inhibit cell wall biosynthesis through noncompetitive inhibition of the (1 → 3)-β-D-glucan synthase complex. This target is unique to fungi, thus contributing to the favorable toxicity profile of echinocandins [1].

The contemporary echinocandins originated as early as 1974, when the parent compound (echinocandin B) for anidulafungin was identified [2]. This was followed in 1989 by discovery of the compound that led to caspofungin (MK-991), and the precursor of micafungin (FK-463) was identified in 1990 [3,4]. Caspofungin was approved in January 2001 by the US Food and Drug Administration (FDA) for the treatment of invasive fungal infections (IFIs) in adults (July 2008 for use in children >3 months of age), followed by micafungin and anidulafungin (approved in March 2005 and February 2006, respectively).

CHEMISTRY

The echinocandins are lipopeptides that have been synthetically modified from the fermentation broths of various fungi. All molecules in clinical use or development are amphiphilic cyclic hexapeptides with an N-linked acyl lipid side-chain and a molecular weight of approximately 1200 [5].

Caspofungin is derived from Glarea lozoyensis. It is a 1-[(4R, 5S)-5-[(2-aminoethyl) amino]15-N2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3R)-3-hydroxy-L-ornithine] pneumocandin B0 diacetate. Its molecular formula is C_{52}H_{88}N_{10}O_{15} × 2 C_{2}H_{4}O_{2}, and its molecular weight is 1213.42 [6] (Figure 1A).

Micafungin is derived from Coleophoma empetri through cleavage of a naturally occurring hexapeptide from the fungus and the addition of fatty-α-acyl side-chain. Micafungin sodium is chemically designated as pneumocandin A0, 1-[(4R, 5R)-4, 5-dihydroxy-N2-[4′-(pentyloxy)phenyl]-3′-24 isoxazolyl][benzoyl]-1-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy) phenyl]-25 i-threonine], monosodium salt. Its molecular formula is C_{56}H_{70}N_{9}NaO_{23}S, and its molecular weight is 1292.26 [8] (Figure 1B).

Anidulafungin is derived from Aspergillus nidulans. It is a 1-[(4R, 5R)-4,5-dihydroxy-N2-[[4′-(pentyloxy) [1,1′:4′, 1′-terphenyl]-4-yl] carbonyl]-1-ornithine] echinocandin B. Its molecular formula is C_{58}H_{73}N_{7}O_{17}, and its molecular weight is 1140.2 [9] (Figure 1C).

MECHANISM OF ACTION

The echinocandins work at the level of the cell wall of fungi inhibiting (1 → 3)-β-D-glucan synthesis. Specifically, they
bind to (1 → 3)-β-D-glucan synthase, an enzyme complex within the fungal cell wall comprised of at least 2 subunits: FKS1p (encoded by the genes FKS1, FKS2, and FKS3) and Rho1p. FKS1p transcription is linked to cell wall remodeling 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 [10–12]. This inhibition results in fungicidal activity against Candida species. However, 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 predominates in Candida albicans and Aspergillus fumigatus, while Zygomycetes lack this component [13]. Inhibition of Aspergillus species with caspofungin and others echinocandins results in profound changes in the growth, morphology, and cell wall structure of hyphae [14].

With Aspergillus fungi, exposure to echinocandins causes hyphae to grow irregularly, with many branched tips, disrupted hyphae, and distended cells. In Candida fungi, cells become greatly enlarged and distorted, with aberrant daughter cell and chlamydomspore-like formation and, ultimately, lysis of the cell membrane [14–16].

**SPECTRUM OF ACTIVITY**

In vitro susceptibility testing of antimicrobial agents should predict the in vivo response to therapy. The in vitro susceptibility of an infecting organism to the antimicrobial agent selected for therapy is one of several factors that influence the likelihood that therapy for an infection will be successful [17].

The minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent that inhibits the growth of fungi, as established by a standardized endpoint. The minimum effective concentration (MEC) is defined as the lowest concentration of an echinocandin that results in growth of filamentous fungi producing conspicuously aberrant growth. Aberrant growth of hyphae is defined as small, round, compact microcolonies compared with the hyphal growth in the control well that does not contain an antifungal agent.

There are 2 reference methods for broth microdilution antifungal susceptibility testing of echinocandins against Candida species: Clinical and Laboratory Standards Institute (CLSI) method [18] and the European Committee on Antimicrobial Susceptibility Testing method [19]. Both use a 24-hour duration
of inoculation and a prominent inhibition (50% relative to growth control) MIC endpoint criterion, but differ in the physical platform employed, inoculum density, glucose content of medium, and method of endpoint MIC reading. Although these are 2 different methods, caspofungin has yielded similar MICs with essential agreements (±2 dilutions) of 98% [20].

In 2011, the CLSI established new Candida species–specific clinical breakpoints not only for echinocandins, but also for azoles (fluconazole and voriconazole). This change was made due to the recognition that MICs for the various agents were significantly lower for some species than others and that the previous clinical breakpoints (<2 µg/mL for echinocandins) were not appropriate for all species [18].

**CANDIDA SPECIES**

All 3 echinocandins in vivo and in vitro are fungicidal against Candida species, including those that are known to be intrinsically resistant to triazoles (C. glabrata, C. krusei) or amphotericin B (AmB) (C. lusitaniae). In recent years, increasing numbers of rare Candida species have been reported in clinical cases; some of them are susceptible to echinocandins (C. famata, C. rugosa), whereas others are less susceptible to this class (C. fermentati and C. guillermondii) [21–23]. Globally, the minimum inhibitory concentration required to inhibit the growth of 50% of a microorganism of the echinocandins against Candida is ≤0.5 µg/mL, and the minimum inhibitory concentration required to inhibit the growth of 90% of a microorganism (MIC90) is <2 µg/mL. MICs for C. lusitaniae and C. parapsilosis were higher than those for C. albicans [24–26].

**ASPERGILLUS SPECIES**

Echinocandins have a specific form of activity against Aspergillus species, causing damage to the hyphal tips and branch points of growing cells, thus decreasing invasion. The potency of echinocandins may be further augmented by immunomodulatory activity resulting from release or unmasking of cell wall glucans, leading to dectin-1–dependent, proinflammatory enhancement of macrophage and neutrophil killing activity [27].

Although fungistatic against Aspergillus species, the echinocandins exhibit excellent in vitro and in vivo activity against many Aspergillus species, including A. fumigatus, A. flavus, A. niger, and A. terreus [28–30]. MICs are difficult to determine for echinocandins against Aspergillus species, and MEC may be a better measure of susceptibility of Aspergillus [13]. (1 → 3)-β-D-glucan is incorporated at the apical growing tips of Aspergillus hyphae, which is the location where echinocandins exert their effect, leading to characteristic swollen, stubby hyphae and clumping when visualized on microscopy. The MEC for caspofungin against A. fumigatus is ≤0.25 µg/mL, and the MEC for micafungin and the MIC90 for anidulafungin are ≤0.125 µg/mL [31–33]. In a study from Pfaffer et al, 526 isolates confirmed that the inhibitory activities of all 3 agents were comparable, although MECs of micafungin and anidulafungin were 2- to 10-fold lower than for caspofungin [29].

**OTHER FUNGI**

Echinocandins are not active as single agents against Mucorales, Fusarium species, or Scedosporium species (due to diminished (1 → 3)-β-D-glucan synthase activity) or against Trichosporon species and Cryptococcus neoformans (due to predominantly (1 → 6)-β-D-glucan linkages) [1]. Although echinocandins are active against the mycelial forms of dimorphic fungi, MICs are high enough for the yeast forms; thus, with this evidence their use should be avoided for the treatment of infections caused by these fungi [30].

**PHARMACOKINETICS**

Echinocandins share similar spectra of in vitro antifungal activity; however, each agent differs in its pathway of metabolism, resulting in distinguishable half-lives, drug interactions profiles, and dosing strategies [12, 34]. The echinocandins have >99% of protein binding and, as a result, 1% of the echinocandin is excreted unchanged in the urine [12, 23]. Although echinocandins do not achieve high urine concentrations, there have been case reports of sterilization of urine after the use of echinocandins in resistant-to-azoles candiduria by achieving high concentrations of echinocandins in the tissue [35–37]. These observations are compatible with studies of echinocandins in successful treatment of experimental renal candidiasis [38–41]. In addition, the echinocandins are not dialyzable; therefore, supplemental doses after dialysis are not required. The predominant pharmacokinetic differences among the 3 agents are metabolism and half-life (terminal half-life of 27–50 hours for caspofungin, 15 hours for micafungin, and 40–50 hours for anidulafungin) [42, 43]. Echinocandins distribute well into the tissues, including lung, liver, and spleen, but with minimal penetration into central nervous system (CNS) tissues, including the eye, due to their high protein binding and large molecular weight. Degradation products are excreted over many days, primarily via bile [6].

**CASPOFUNGIN**

Caspofungin is a highly protein-bound (>95%) drug with extensive distribution in tissues. Caspofungin degrades spontaneously and also undergoes hepatic metabolism via spontaneous peptide hydrolysis and N-acetylation [34]. Biliary caspofungin concentrations are reportedly 30% that of serum [12]. The major degradation product is not removed with hemodialysis, and
no dose adjustments are recommended for renal insufficiency or failure requiring hemodialysis [42]. Following an initial intravenous infusion, tissue distribution accounts for an initial rapid fall in plasma levels, followed by gradual re-release of drug from extravascular tissues coupled with slow hepatic metabolism; caspofungin exhibit dose-proportional plasma pharmacokinetics with a β half-life of 10–15 hours that allows for once-daily dosing [44]. A loading dose of 70 mg, leading to mean steady-state concentrations >1 µg/mL at day 1, followed by a 50-mg once-daily dose, is therefore required to attain an initial therapeutic plasma level and avoid drug accumulation [11, 44, 45].

In children aged 3 months to 17 years, the recommended dose is 50 mg/m²/day (maximum 70 mg), following a loading dose of 70 mg/m², in comparison to that of adults at 50 mg daily. Clearance is lower in neonates and adults, and increased during childhood. These differences may be determined by the differential rate of distribution from plasma into hepatic tissue [1, 45].

**ANIDULAFUNGIN**

Single-dose intravenous administration of anidulafungin 35–100 mg to healthy volunteers shows linear pharmacokinetics, with maximum concentration (Cmax) ranging from 1719 ng/mL to 3825 ng/mL, a large volume of distribution (Vd) of 0.72–0.9 L/kg, and long half-life of approximately 40 hours [16] (Table 1).

In children, differences in clearance based on age have not been found for anidulafungin, unlike caspofungin and micafungin [1]. A single study of safety and pharmacokinetics (PK) of 25 neutropenic children demonstrated that dosages of 0.75 mg/kg and 1.5 mg/kg for those 2–17 years of age have similar PK as doses of 50 mg or 100 mg per day in adults. Clearance is lower in neonates and adults, and increased during childhood. These differences may be determined by the differential rate of distribution from plasma into hepatic tissue [1, 45].

**MICAFUNGIN**

Micafungin exhibits linear PK over the therapeutic dosing range of 50–150 mg once a day. No loading dose is required, and doses of 100 mg and 150 mg provide trough concentrations of approximately 2 µg/mL and 2.5 µg/mL on day 1 of therapy [46]. Micafungin is metabolized into 3 metabolites: M1, M2, and M5. The M1 metabolite is formed by metabolism of micafungin by arylsulfatase; M1 is further broken down by catechol-O-methyl-transferase to M2. The third metabolite, M5, is formed as the side-chain of micafungin is hydrolyzed by the cytochrome P450 isoenzymes (mostly Cytochrome P450, family 3, subfamily A) [11, 46] (Table 1).

Dosing for children has been approved by the FDA [51]; data suggest linear PK with an inverse relationship between age and clearance, such that dosages of 3–4 mg/kg once daily for children aged 2–8 years, and 2–3 mg/kg once daily for those aged 9–17 years yield similar exposure of drug observed in adults [52]. Studies in pediatric patients with <15 kg body weight suggest larger volumes of distribution and higher clearance than in children and adults, such that neonatal doses of 10 mg/kg/day may be necessary [53].

Although echinocandins have low levels in cerebrospinal fluid, they achieve sufficiently elevated concentrations in CNS tissue to result in significant reduction of C. albicans in cerebrum and cerebellum in experimental hematogenous Candida meningocerebralitis (HCME) [53]. In experimental HCME, micafungin demonstrated penetration and efficacy in CNS tissue and achieved sufficient concentrations to produce a candidacidal effect. High plasma concentrations of micafungin are required to achieve therapeutic levels in CNS tissues. Drug penetration into the CNS tissue is dependent on the generation of a concentration gradient of sufficient magnitude to drive drug from the plasma into infected brain tissue. With these data, dosages of 8–15 mg/kg for CNS infections in neonates should attain therapeutic levels [1].

**PHARMACODYNAMICS**

The plasma drug concentration profile that optimizes the antifungal efficacy of echinocandins has been only partly elucidated [54]. For Candida species, all 3 drugs display concentration-dependent fungicidal activity over a broad concentration range in vivo, with efficacy that is best correlated with Cmax/MIC or area under the plasma concentration - time curve/MIC ratios, as demonstrated in mice with systemic candidiasis [30, 54–58]. With standard drug doses, serum concentrations of >1 µg/mL are typically attained, leading to consensus for the CLSI clinical breakpoints of <2 µg/mL to designate an isolate.

![Table 1. Pharmacokinetics of Echinocandins in Humans](image-url)

<table>
<thead>
<tr>
<th>Echinocandin</th>
<th>Dose, mg</th>
<th>Cmax, mg/L</th>
<th>AUC0–24, mg × h/L</th>
<th>t½β, h</th>
<th>CLc, mL/min/kg</th>
<th>Vd, L/kg</th>
<th>Protein Binding, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin</td>
<td>50</td>
<td>3.44</td>
<td>44.4–53</td>
<td>24–26</td>
<td>0.16–0.26</td>
<td>0.5</td>
<td>84</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50</td>
<td>7.64</td>
<td>87.9–114.8</td>
<td>10–15</td>
<td>0.15</td>
<td>0.14</td>
<td>96–97</td>
</tr>
<tr>
<td>Micafungin</td>
<td>50</td>
<td>10.9</td>
<td>111.3</td>
<td>11–17</td>
<td>0.16–0.185</td>
<td>0.22–0.24</td>
<td>99.8</td>
</tr>
</tbody>
</table>

Sources: [23, 46–49].
Abbreviations: AUC0–24, area under the plasma concentration - time curve; CLc, total clearance; Cmax, maximum concentration; t½β, beta elimination half-life; Vd, volume of distribution.
as susceptible [59]. The postantifungal effect (PAFE) presented by the echinocandins against C. albicans was noted to be >12 hours when concentrations exceeded the MIC [13, 57]. The PAFE for micafungin against Candida species ranged from 0.9 hour to >20.1 hours depending upon the concentration; this means concentrations 4 times above the MIC produce the longest PAFE [60]. For anidulafungin, PAFEs of >12 hours have also been observed [57]. An in vivo murine model study of caspofungin pharmacodynamics demonstrated that therapeutic concentrations of the drug persist at the site of the infection in kidney tissue well after the serum concentration falls below the MIC [58].

The pharmacodynamic parameters for killing or inhibiting Aspergillus species are not clearly defined. The efficacy of their fungistatic concentration-dependent activity is best correlated with Cmax/MEC ratios [61]. Published in vivo studies to define the pharmacodynamic properties of echinocandins against Aspergillus species are sparse, but also suggest that an Eagle effect may occur with this organism [62, 63]. Two murine models of experimental invasive pulmonary aspergillosis have documented concentration-dependent activity in neutropenic mice administered caspofungin and correlation of the Cmax/MEC with reduction in fungal burden in the lungs [62]. Lewis and colleagues noted a slight paradoxical increase in Aspergillus growth by using caspofungin compared with micafungin in a neutropenic mice model. Both drugs showed a dose-dependent reduction in fungal burden; however, a steeper dose-response curve was seen on caspofungin doses >4 mg/kg day exhibiting a paradoxical increase in fungal load [63]. Petrakis et al demonstrated a dose-dependent response in survival to micafungin, despite a lack of clearance of A. fumigatus from the lungs, as well as a reduction in the level of pulmonary infarction in persistently neutropenic rabbits with invasive pulmonary aspergillosis [38]. Similar results were seen years later in neutropenic murine models, where the survival benefit from micafungin dose-dependent response was observed [63, 64].

Limited data are available regarding the pharmacodynamic properties of echinocandins against pathogens other than Candida species and Aspergillus species; caspofungin has been shown to reduce Rhizopus oryzae burden in the brain and improve survival in mice at low but not at high doses [65].

COMBINATION THERAPY

The unique mechanism of the echinocandins has generated much interest in their use in combination antifungal regimens, particularly for invasive aspergillosis (IA). On earlier clinical experimental studies, the combination of different antifungal drugs has shown promising results in both in vitro and in animal models.

Perea et al presented an in vitro study showing a synergistic interaction between caspofungin and voriconazole while using 48 clinical Aspergillus isolates obtained from patient samples with IA [66].

Petrakis et al demonstrated that the combination of micafungin plus ravuconazole exerted effect in vitro and in vivo as proof of concept of the potential additive to synergistic interactions between triazoles and echinocandins against A. fumigatus [67]. The combination of anidulafungin plus voriconazole resulted in improved survival compared with either monotherapy in some animal models [68]. Furthermore, Petrakis et al in another study presented in vitro and in vivo correlations of the additive to synergistic interaction of the regimen with anidulafungin plus voriconazole in treatment of invasive pulmonary aspergillosis in persistently neutropenic rabbits. High dosages of echinocandins (10 mg/kg/day) resulted in antagonism, suggesting that higher dosages of an echinocandin may be a deleterious combination [69]. Depending on experimental conditions, not all in vivo studies consistently support the synergistic interaction of triazole plus echinocandin. Kirkpatrick et al found that the combination of voriconazole plus caspofungin was not superior to that of voriconazole alone [70].

In clinical series, there have been several retrospective clinical studies characterizing a combination therapy for IA; however, most of them are related to a combination strategy based on AmB combined with different antifungals (either triazoles or echinocandins), and few studies are reported with an echinocandin plus triazole combination. Upton et al presented a retrospective study from cases of proven and probable IA diagnosed in hematopoietic cell transplant recipients. No differences in outcomes were seen in patients who received a combination therapy (voriconazole plus caspofungin), compared with those who received voriconazole monotherapy (hazard ratio [HR], 2.3; 95% confidence interval [CI], 0.6–9.4; P = .23) [71].

Previously, Marr and colleagues reported on 47 patients with evidence of progressive infection after ≥7 days with AmB; 31 patients were treated with voriconazole (as monotherapy), and the remaining 16 patients were given combination therapy with voriconazole plus caspofungin. The patients who received combination therapy had a significantly lower rate of mortality compared with those who received voriconazole alone (odds ratio, 0.28; 95% CI, 0.08–2.78) [72]. Also, 3-month survival after the start of salvage therapy (either voriconazole or combination therapy) was greatest among the group of patients who received the combination regimen (HR, 0.43; 95% CI, 0.17–1.11; P = .050).

Singh et al in a retrospective study evaluated 40 solid organ transplant recipients who received a combination of voriconazole and caspofungin as primary therapy for IA compared with a control group of 47 patients who received liposomal AmB as primary therapy; reduced mortality in the subset of patients with A. fumigatus infection was seen in the combination group (adjusted HR, 0.37; 95% CI, 0.16–0.84). In addition,
combination therapy in this study was independently associated with improved 90-day survival in multivariate analysis [73].

Recently, a randomized controlled trial (RCT) based on the preclinical and earlier clinical data was conducted to test the hypothesis of combination therapy of echinocandin and triazole against IA. This study, which enrolled 270 patients with IA, compared voriconazole as monotherapy vs a combination with voriconazole plus anidulafungin. There was a trend toward improved fungus-free 6-week survival on the primary endpoint for survival in the combination group compared with standard monotherapy [74]. Six-week mortality was 19.3% for combination therapy and 27.5% for monotherapy (95% CI, −19.1 to 1.5). In a post hoc analysis of a group of 222 patients with probable IA (radiographic abnormalities and a positive serum or bronchoalveolar lavage fluid for galactomannan antigen), a statistically significant difference in mortality was observed (16% with combination therapy vs 27% with the voriconazole monotherapy; 95% CI, −22.7 to −4.4) [74]. That this study was underpowered and had relatively limited follow-up may have prevented it from definitively testing the hypothesis that triazole-echinocandin combination therapy is superior to the triazole alone in treatment of IA.

PROPHYLAXIS

The role of echinocandins in antifungal prophylaxis has been studied in the setting of hematopoietic stem cell transplantation (HSCT), liver transplantation, and following surgery.

An RCT, comparing micafungin and fluconazole as prophylaxis in neutropenic adults and children following autologous and allogeneic HSCT, demonstrated efficacy of an echinocandin for prophylaxis (80% for micafungin vs 74% in the fluconazole arm) [75]. A smaller RCT of 104 HSCT recipients also compared micafungin vs fluconazole for prophylaxis; no difference in the prevention of IFIs was detected [76].

In a retrospective analysis of HSCT recipients receiving caspofungin prophylaxis (35–50 mg/day; median duration 73 days), breakthrough IFIs occurred in 7.3% of patients; the majority of these were due to molds, diagnosed at a median of 65 days after starting prophylaxis [77]. These findings suggest that both micafungin and caspofungin are valuable options for antifungal prophylaxis in HSCT recipients.

Caspofungin has also been evaluated in a small number of patients in the setting of secondary antifungal prophylaxis (ie, patients with history of previous IFI) during HSCT. Only 2 of 18 patients with IFI in one study developed progressive disease while receiving the agent after transplantation and during the 1-year follow up [78].

Liver transplant recipients are considered another group at high risk for IFIs. This includes those who require retransplantation due to graft dysfunction, patients undergoing renal replacement therapy, and those with prior fulminant hepatitis; the incidence of IFI without prophylaxis is estimated in 20% without antifungal 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. Of 71 patients, 2.8% developed an IFI 19–41 days after cessation of caspofungin [79].

Micafungin is the only echinocandin that has been evaluated for fungal prophylaxis in pediatric HSCT recipients. In 2001, Mehta et al from the Children’s Hospital Medical Center in Cincinnati reported that alternate-day micafungin dosing may provide an attractive alternative for antifungal prophylaxis in HSCT in children aged ≤10 years [80].

ADVERSE EFFECTS

Echinocandins are well tolerated, and all the 3 members of the class have similar types of adverse effects. Serious adverse effects requiring drug discontinuation occur less frequently with the echinocandins than with other classes of systemic antifungals. Elevations of aminotransferases and alkaline phosphatase are the most frequently reported laboratory abnormalities, but are less common compared with those receiving azoles or AmB formulations [6, 13].

Histamine release is a frequent biological effect for basic polypeptide compounds. Most of the histaminic reactions have been reported with anidulafungin when the drug is infused at a rate that exceeds 1.1 mg/minute. Although rash, pruritus, hypotension, bronchospasm, and angioedema are the symptoms related to echinocandins adverse effects, these effects are transient and are easily managed by slowing the infusion rate and providing supportive care [9, 12]. Injection site pain, noncomplicated gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), and hematologic effects (anemia, leukopenia, neutropenia, and thrombocytopenia) represent <10% overall of adverse effects [6, 8, 9].

Treatment of IFIs in critically ill hospitalized patients is a formidable challenge for clinicians. At the beginning of the century [81], echinocandins were included within the limited armamentarium of antifungal agents. Fifteen years later, these compounds have proven to be essential agents in the treatment of deeply invasive candidiasis. This class of antifungals that are safe, well tolerated, and with favorable pharmacokinetic and pharmacodynamics profiles is expanding our understanding of synergistic combinations of 2 different classes of antifungal agents that will advance our understanding of antifungal therapy.

Notes

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