

Antifungal Therapy for Invasive Fungal Diseases in Allogeneic Stem Cell Transplant Recipients: An Update

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Abstract Invasive fungal diseases (IFDs) remain a major cause of morbidity and mortality in allogeneic stem cell transplant (SCT) recipients. While the most common pathogens are *Candida* spp. and *Aspergillus* spp., the incidence of infections caused by non-*albicans* *Candida* species as well as molds such as Zygomycetes has increased. For many years, amphotericin B deoxycholate (AMB-D) was the only available antifungal for the treatment of IFDs. Within the past decade, there has been a surge of new antifungal agents developed and added to the therapeutic armamentarium. Lipid-based formulations of amphotericin B provide an effective and less nephrotoxic alternative to AMB-D. Voriconazole has now replaced AMB-D as first choice for primary therapy of invasive aspergillosis (IA). Another extended-spectrum triazole, posaconazole, also appears to be a promising agent in the management of zygomycosis, refractory aspergillosis, and for prophylaxis. Members of the newest antifungal class, the echinocandins, are attractive agents in select infections due to their safety profile, and are a more attractive option compared to

AMB-D as initial treatment for invasive candidiasis and (based on one study) challenge fluconazole for superiority in management with this mycoses. However, challenges do exist among these newer agents in very high-risk individuals like allogeneic SCT recipients, which may include adverse drug events, drug–drug interactions, variability in oral absorption, and availability of alternative formulations. The addition of newer agents has also stimulated interest in the potential application of combination therapy in serious, life-threatening infections. However, adequate studies are not available for most IFDs; thus, the clinical use of combination therapy is not evidenced based on most cases and preciseness in its use is uncertain. Finally, therapeutic drug monitoring of select antifungals (notably posaconazole and voriconazole) may play an increasing role due to significant interpatient variability in serum concentrations after standard doses.

Keywords Invasive fungal diseases · Antifungals · Allogeneic stem cell transplant · Amphotericin B · Triazoles · Echinocandins

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Introduction

Invasive fungal diseases (IFDs) remain a major cause of morbidity and mortality in allogeneic stem cell transplant (SCT) recipients [1, 2]. While the overall

incidence of IFDs has increased in this patient population throughout the last two decades [3], the most common etiologies of IFDs continue to be *Candida* spp. and *Aspergillus* spp. [4]. Invasive candidiasis has been reported in approximately 5% of allogeneic SCT recipients [5]. While the majority of candidal infections are due to *C. albicans* [4], the incidence of infections caused by non-*albicans Candida* spp., particularly *C. glabrata* and *C. krusei* have increased over the last 10 years [6]. It has been proposed that the widespread use of fluconazole as a prophylactic regimen has contributed (at least in part) to this changing landscape, and in a large cancer center, these two species have become the two leading causes of candidemia [7]. With the frequent use of extended-spectrum azoles, *C. krusei* may be less frequent but it is likely that *C. glabrata* will still be an important yeast to cause disease in allogeneic SCT recipients. IFDs caused by molds such as *Aspergillus* and Zygomycetes are also important complications of allogeneic SCT. A multicenter survey reported incidence rates of invasive aspergillosis (IA) in allogeneic SCT recipients between 2.3% and 3.9%, while survival rates are less than 15% in this highly compromised population, especially those with proven infections [8, 9]. However, outcomes of IA may be improving. Twelve-week mortality rate of 35.5% (38/107 patients) was reported in a recent multicenter, observational study [10]. On the other hand, zygomycosis constituted 4.9–20% of invasive mold infections in allogeneic SCT recipients, while crude mortality in these patients has been reported as high as 91% [1, 10–12].

Amphotericin B deoxycholate (AMB-D), a polyene, was first used in the 1950s and (for many years) was the only available antifungal for the treatment of serious IFDs. Flucytosine, an oral antifungal agent, was added to the antifungal formulary in 1971, but was seldom employed in this population due to its limited antifungal spectrum, rapid development of resistance (when used as monotherapy), and its associated toxicities (notably gastrointestinal and hematologic). Twenty years later, the azoles, fluconazole and itraconazole, were approved for IFD use in the United States. This was followed in the late 1990s by the availability of three lipid-based formulations of amphotericin B. Since 2000, several new antifungal agents have become available. A new class of antifungals (the echinocandins) was introduced. Members of

this class include caspofungin, micafungin, and anidulafungin. In addition, extended-spectrum triazoles, voriconazole and posaconazole, were recently approved for clinical use [13] and specifically target some of the important IFDs found in allogeneic SCT.

The objective of this article is to review the clinical application of the various options for the treatment of IFDs in allogeneic SCT recipients. Our focus will be on the data describing the most recent antifungal agents added to our armamentarium.

Amphotericin B

For years, AMB-D was the treatment of choice for many serious, life-threatening IFDs in allogeneic SCT. Amphotericin B targets the fungal cytoplasmic membrane by binding to sterols in the fungal cell membrane to create ionic pores, resulting in loss of membrane potential and subsequent collapse [14]. Today, amphotericin B remains the broadest-spectrum fungicidal agent. Most yeasts and molds are susceptible in vitro, including most *Candida* spp., *Aspergillus* spp., Zygomycetes, *Cryptococcus* spp., and some agents of hyalohyphomycosis. Intrinsic resistance of amphotericin B is infrequent, but may include species such as *A. terreus* [15, 16], *C. lusitanae* [15, 17], and the *Scedosporium* spp. [15].

Requirement for parenteral administration, along with a high incidence of treatment-related adverse events [i.e., infusion-related reactions, electrolyte imbalances (including hypokalemia and hypomagnesemia), and nephrotoxicity] limit the widespread use of AMB-D. A variety of clinical strategies aimed at reducing such toxicities have been employed, including administration of premedications such as diphenhydramine, acetaminophen, and meperidine (to reduce fever, chills, and rigors), electrolyte replacement, and infusion of saline prior to and/or immediately following AMB-D (i.e., “sodium loading”) [18, 19]. Most recently, studies have examined the application of continuous infusion of AMB-D in an attempt to reduce the incidence of nephrotoxicity [20–22]. In one such evaluation, a retrospective study reported significant reductions in toxicity resulting from continuous infusion of AMB-D than a 4-h infusion (10% vs. 45%; $P < 0.001$) in high-risk hematology patients, including bone marrow transplant recipients [21]. Despite this improved safety,

lack of efficacy data in patients with documented IFDs, need for a dedicated intravenous line, and failure to capitalize on the dose-related pharmacodynamic properties of amphotericin B [23] presently limit the use of continuous infusions of AMB-D. In our opinion, the nephrotoxicity issues in allogeneic SCT recipients already at risk with calcineurin inhibitors make AMB-D an unattractive agent in this population, particularly when safer preparations of amphotericin B exist.

Three lipid-based formulations of amphotericin B were developed in order to minimize toxicities associated with AMB-D, in particular, nephrotoxicity. Available formulations include amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-AMB) [19]. A detailed discussion of the differences between these preparations is provided elsewhere [24], and is beyond the scope of this article. However, all lipid-based formulations of amphotericin B have shown decreased rates of nephrotoxicity when compared to AMB-D [25–30]. Pharmacokinetic differences exist among lipid-based formulations of amphotericin B. For example, L-AMB achieves higher peak plasma concentrations in the serum and area under the time–concentration curve compared to both ABLC and ABCD [31]. In contrast, animal studies have reported more rapid delivery of ABLC and ABCD to the lung when compared to L-AMB [31, 32]. Differences in adverse effects between lipid-based formulations of amphotericin B have been reported. L-AMB was reported to have a reduction in nephrotoxicity and reduced day 1 infusion-related toxicities when compared to ABLC for empiric treatment of febrile neutropenia [33]. In contrast, ABCD has been associated with an increased incidence of infusion-related toxicities when compared to AMB-D [26].

The clinical efficacy of AMB-D for treatment of IFDs has been demonstrated in numerous controlled clinical trials [29, 34–36]. More recently, lipid-based formulations of amphotericin B (most notable for L-AMB and ABLC) have demonstrated efficacy in the treatment of invasive candidiasis, IA, and zygomycotic infections [37–39]. L-AMB was found to possess equivalent efficacy to an echinocandin for invasive candidiasis, but with an increased incidence of adverse events [37]. Current treatment guidelines for many forms of IFDs (notably for candidiasis, aspergillosis,

and many endemic mycoses) continue to identify various formulations of amphotericin B as treatment options in severe, refractory infections [40–42]. Amphotericin B is one of the few available antifungal agents which has consistent activity against most Zygomycetes, and a recent study demonstrated that delays in the institution of amphotericin B therapy impacts significantly on mortality in such infections [43]. It is likely that in allogeneic SCT recipients, these formulations are more commonly selected in patients with prior exposure or failure to azoles or echinocandins, or as the standard primary therapy when definite or predicted zygomycosis cases are diagnosed.

Despite several decades of clinical use, the optimal doses of amphotericin B preparations are unknown. Dosing recommendations for the various antifungal agents including amphotericin B preparations are presented in Table 1. Doses of AMB-D for treatment of IFDs generally range from 0.6 to 1.5 mg/kg/day, with the highest doses generally reserved for the treatment of refractory, life-threatening disease (such as IA unresponsive to voriconazole or for the treatment of zygomycosis). These higher doses dramatically increase the risk of treatment-related toxicity in allogeneic SCT patients. Doses for lipid-based formulations of amphotericin B generally range between 3 and 5 mg/kg/day. Since amphotericin B has demonstrated concentration-dependent pharmacodynamic properties [44, 45], increases in doses have recently been investigated in attempts to optimize efficacy. Neutropenic patients and those who had undergone allogeneic SCT with confirmed invasive mold infections ($n = 201$) were randomized to either L-AMB 3 or 10 mg/kg/day for 14 days, followed by 3 mg/kg/day thereafter [38]. While no difference in clinical response in the first 14 days could be detected, higher rates of nephrotoxicity and hypokalemia were noted in the 10-mg/kg group. This study suggests that for primary therapy, very high doses are not necessary for success. Thus, in light of these data, the clinician must still judge the cost–benefit ratio of choosing doses for the various amphotericin B formulations (until further, more precise dosing studies are performed), even though very high doses have not yet shown superiority. In addition, clinicians must carefully weigh the potential benefit of reductions in treatment-related nephrotoxicity with the increased acquisition cost when choosing a lipid-based formulation over AMB-D [46].

Table 1 Dosing recommendations for antifungal agents used in the management of invasive fungal diseases

Antifungal agent	Dose	Dosage adjustment required for hepatic impairment?	Dosage adjustment required for renal impairment?
Polyenes			
AMB-D	0.6–1.5 mg/kg/day IV	No	No
Lipid-based formulations of amphotericin B	3–5 mg/kg/day IV	No	No
Azoles			
Voriconazole	IV: 6 mg/kg twice daily on day 1, followed by 4 mg/kg twice daily PO: 400 mg twice daily on day 1, followed by 200 mg twice daily ^a	Yes. Reduce maintenance dose by 50% in patients with mild to moderate hepatic impairment	IV formulation not recommended in patients with a CrCl < 50
Posaconazole	200 mg PO three times daily ^b	No	No
Echinocandins			
Caspofungin	70 mg IV on day 1, followed by 50 mg daily	Yes. Reduce maintenance dose to 35 mg daily in patients with moderate impairment	No
Micafungin	100 mg IV daily ^c 100–150 mg IV daily ^d	No	No
Anidulafungin	200 mg IV on day 1, followed by 100 mg daily	No	No

AMB-D amphotericin B deoxycholate, IV intravenous, PO orally, CrCl creatinine clearance

^a Dose of voriconazole can be increased to 300 mg po q12h if response to therapy is inadequate

^b Treatment for refractory invasive fungal diseases is 400 mg twice daily, but if there is therapeutic need for best exposure to posaconazole, it should be administered as 200 mg four times daily. Administer with a high-fat meal or nutritional supplement

^c Treatment of candidemia

^d Treatment of invasive aspergillosis

Triazoles

Triazoles act by inhibiting the synthesis of ergosterol through the inhibition of CYP-450-dependent lanosterol 14 α -demethylase which leads to the inhibition of cell growth or cell death [14]. After its introduction, fluconazole rapidly became widely used in the prevention and treatment of candidiasis in a variety of patient populations (including allogeneic SCT recipients) primarily due to its favorable safety profile, high oral bioavailability, and activity against *Candida* spp. (notably *C. albicans*). Its use in prophylaxis for allogeneic SCT recipients improved both morbidity and mortality [47–49]. It is still considered a viable treatment option in the treatment of susceptible *Candida* spp., notably *C. albicans*. However, recent increases in the incidence of non-*albicans* *Candida* spp. (notably *C. glabrata* and *C. krusei*) in hematological

malignancies and bone marrow transplants over the last 10 years has raised concerns about its continued role as initial empiric therapy for invasive candidiasis in this high risk population. Furthermore, the potential for break through yeast infections in high-risk patients receiving fluconazole prophylaxis continues to be an issue in SCT recipients [50]. Itraconazole is also available for the prevention and treatment of a variety of IFDs. However, despite its increased activity in vitro against *Aspergillus* spp., the lack of reliable oral absorption, recent withdrawal of the intravenous formulation, drug–drug interactions, and the adverse event profile of itraconazole oral solution (most notably gastrointestinal intolerance) has limited its widespread use [51] and has generally been replaced by voriconazole and posaconazole in allogeneic SCT recipients.

Voriconazole

Voriconazole was first approved by the FDA in 2002 [14]. It demonstrates a broad spectrum of activity in vitro against most *Candida* spp. (including non-*albicans Candida* spp. such as *C. krusei*), *Aspergillus* spp., *Scedosporium apiospermum*, *Fusarium* spp., *Cryptococcus* spp., and dimorphic fungi. It, like most available agents, does not directly impact the dreaded mold infections in allogeneic SCT, *Scedosporium prolificans* and Zygomycetes. While voriconazole has demonstrated activity in vitro against fluconazole-resistant *Candida* spp., cross-resistance can and will occur and this is particularly true with *C. glabrata* [6].

Voriconazole is available in both intravenous and oral dosage forms. The oral formulation exhibits excellent bioavailability (>90%) [52]. However, in contrast to posaconazole, concomitant administration of fatty foods with oral voriconazole decreases its bioavailability to 80% [52]. For intravenous voriconazole, a loading dose of 6 mg/kg twice daily on day one is followed by 4 mg/kg twice daily [53]. For oral voriconazole, the typical dosing regimen is a loading dose of 400 mg twice daily on day one, followed by 200 mg twice daily [53]. The dose can be increased to 300 mg twice daily in patients whose response to therapy is inadequate [53] or if serum concentrations are too low. Dosage adjustments for the oral formulation are not required in patients with renal impairment [54]. However, the intravenous formulation is not recommended for use in patients with a creatinine clearance <50 ml/min due to concerns regarding potential accumulation of the sulfobutyl ether β -cyclodextrin sodium vehicle [54]. In patients with mild to moderate hepatic impairment (Child-Pugh scores A and B), maintenance doses of voriconazole need to be reduced by 50% following a standard loading dose [54]. The use of voriconazole is discouraged in patients with severe hepatic impairment [53] and its use in this population will need to be a bedside decision.

Voriconazole has demonstrated efficacy for the treatment of a variety of IFDs. In non-neutropenic patients with candidemia, a randomized study demonstrated non-inferiority of voriconazole to AMB-D [55]. Patients with IA treated with voriconazole had significantly better treatment outcomes at week 12 compared to those patients treated with AMB-D

(success rates of 53% vs. 32%; $P < 0.0001$) as well as a better survival (70.8% vs. 57.9%; $P = 0.02$) in a randomized, open-label study [56]. For the subset of allogeneic SCT patients, successful outcomes were 32.4% and 13.3% in the voriconazole and AMB-D groups, respectively. Largely due to these results, voriconazole has become the drug of choice for primary treatment of IA [40]. Although, it should be pointed out that there was still a substantial failure rate in both groups with the agent and the SCT individual still representing great potential for failure.

In addition to treatment, voriconazole has been studied for prophylaxis of IFDs in allogeneic SCT recipients due to its excellent activity against both *Aspergillus* spp. and most *Candida* spp. and is frequently used in allogeneic SCT prophylaxis or off-label when IA risk is considered a possibility [57–59]. A detailed discussion of voriconazole as prophylaxis in allogeneic SCT recipients is beyond the scope of this article, but this agent is frequently intertwined in the management of allogeneic SCT recipients. Recent studies and case reports have shown an increased number of infections caused by Zygomycetes in patients receiving voriconazole for prophylaxis as well as treatment of another mold infection [60–63]. The reason for the increased frequency of zygomycotic infections and the contribution of voriconazole is not clear. Since voriconazole has no in vivo activity against Zygomycetes, it may delay the occurrence of other IFDs (such as aspergillosis) until underlying disease progresses and Zygomycetes can superinfect and produce disease.

Adverse events reported with voriconazole include transient visual disturbances, liver function abnormalities, skin reactions, gastrointestinal complaints, fever, mental confusion, and QT prolongation [52]. Visual disturbances (including abnormal vision, photophobia, color vision changes, or hallucinations) are common in patients treated with voriconazole (14–44%), and typically disappear within the first week of therapy [52]. Mild to moderate elevations in serum transaminases have been reported in 12% of patients receiving voriconazole and may appear after several weeks of therapy [53]. Of note, these abnormalities typically resolved with or without dosage adjustment or discontinuation of the drug [53], but can cause confusion regarding clinical issues such as venous occlusive disease of the liver in SCT recipients. Cases of jaundice

and rare cases of severe hepatitis have been associated with voriconazole [53]. However, most patients had other serious concomitant underlying conditions (such as hematological malignancy) [53], which make it difficult to determine the impact of the azole on clinical deterioration. It is recommended that liver function tests be monitored prior to and intermittently during therapy with voriconazole in high-risk patients. Skin reactions (ranging from mild photosensitivity reactions to Stevens–Johnson syndrome) have been reported in 7% of patients in clinical trials [53]. Similar to other azoles, voriconazole has been associated with QT prolongation. Cases of arrhythmias, cardiac arrests, and sudden deaths have been reported in clinical trials and postmarketing surveillance [53].

Voriconazole is a substrate for, and an inhibitor of, the CYP450 enzyme system, specifically 2C19, 2C9, and 3A4 [52]. As seen with other azoles, interactions with other drugs that are substrates/inhibitors/inducers of the same CYP450 enzyme systems are expected [64]. Voriconazole has the potential to interact with several classes of drugs such as antiretrovirals, immunosuppressants, anticonvulsants, and chemotherapeutic agents [52, 65]. Table 2 lists some of the most significant drug–drug interactions seen with voriconazole, along with posaconazole and the echinocandins. In comparison to the other azole agents as well as the other antifungal classes, voriconazole appears to have the greatest risk for drug–drug interactions [66].

Voriconazole serum concentrations can be highly variable due to a non-linear kinetic profile, numerous drug–drug interactions, influence of food, and the genetic polymorphisms of the CYP450 enzyme primarily responsible for metabolism (namely CYP 2C19) [67, 68]. Data examining the associations between voriconazole serum concentrations with clinical outcome and safety are sparse [67, 69–72]. In one report, 10/10 patients with random voriconazole concentrations exceeding >2.05 mg/l experienced a positive clinical outcome [69]. In contrast, 8 of 18 patients with random voriconazole concentrations <2.05 mg/l either died or had disease progression. In another report, 46% (6/13) of patients with serum trough concentrations ≤ 1 mg/l failed to respond to therapy, compared to 12% (5/39) of patients with serum trough concentrations >1 mg/l [67]. In regards to safety, one study found that liver failure or deterioration in liver function developed in 6 of 22

patients with random voriconazole serum concentrations >6 mg/l [70]. Increased neurological adverse events including altered mental status have also been reported in patients with serum trough concentrations >5.5 mg/l [67]. Based on the available information, voriconazole serum concentration monitoring may be clinically useful in select patient populations, such as patients with suspected voriconazole toxicity, concomitant administration of drugs altering voriconazole serum concentrations, or patients who appear to be failing treatment [68]. In those patients, it has been suggested that serum trough voriconazole concentrations be obtained after 1 week of therapy to target voriconazole levels between 2 and 6 mg/l. However, further studies are warranted. Of note, the limited availability of laboratories performing the voriconazole assay may restrict the practicality of routine serum concentration monitoring, but in patients at risk for failure or even in the initial algorithm for management of a severe fungal disease in allogeneic SCT recipients, it should be part of the work up.

Posaconazole

Posaconazole was approved in 2006, with a spectrum of activity most comparable to the other extended-spectrum azole, voriconazole. However, unlike voriconazole, posaconazole demonstrates increased potency in vitro against Zygomycetes, and this may have a therapeutic consequence [13].

Posaconazole is available only as an oral suspension, and the daily dose should be divided due to saturable absorption [73]. Typical dosing of posaconazole for prophylaxis of IFDs (*Candida* and *Aspergillus* infections) is 200 mg three times daily [74]. For refractory IFDs (including IA and zygomycosis), 400 mg is used twice daily [40, 75–77]. Administration of no more than 800 mg daily (given as 200 mg four times daily) provided optimal exposure, but is not FDA-approved. It is recommended that posaconazole be administered with a high-fat meal or nutritional supplement to increase bioavailability [78]. On an empty stomach, the bioavailability of posaconazole ranges from 8% to 47%, while it increases by 400% when the dose is administered with a high-fat meal or nutritional supplement [78]. Since posaconazole is not available as an intravenous preparation, its use may be limited in patients who are unable to take or adequately absorb oral

Table 2 Significant drug–drug interactions encountered with the extended-spectrum azoles and echinocandins [52, 53, 65, 74, 85–87, 92–94, 106–108]

Drug–drug interactions		Recommendation
Azoles		
Voriconazole	Terfenadine, Astemizole, Cisapride, Pimozide, Halofantrine, Quinidine, Sirolimus, Rifampin, Rifabutin, long-acting Barbiturates, Carbamazepine, Ergot Alkaloids, Ritonavir (high dose)	Concurrent administration is contraindicated
	Amiodarone	Avoid concomitant administration if possible or use with close monitoring of amiodarone ^a
	Efavirenz	Increase voriconazole dose and decrease efavirenz dose
	Phenytoin	Increase voriconazole dose
	Tacrolimus, Cyclosporine, Omeprazole (doses > 40 mg/day) Cyclophosphamide ^b	Reduce doses of tacrolimus, cyclosporine, and omeprazole Monitor for signs of cyclophosphamide toxicity
Posaconazole	Terfenadine, Astemizole, Cisapride, Pimozide, Halofantrine, Quinidine, Sirolimus, Ergot Alkaloids	Concurrent administration is contraindicated
	Phenytoin, Rifabutin, Efavirenz	Avoid concomitant administration unless the benefits outweigh the risks
	Tacrolimus, Cyclosporine	Reduce doses of tacrolimus and cyclosporine
Echinocandins		
Caspofungin	Rifampin	Increase caspofungin dose
	Phenytoin, Carbamazepine, Nelfinavir, Efavirenz, Nevirapine, Dexamethasone	Consider increasing caspofungin dose
	Cyclosporine, Tacrolimus	Monitor cyclosporine and tacrolimus levels
Micafungin	Cyclosporine, Tacrolimus, Nifedipine	Monitor levels of cyclosporine and tacrolimus. Monitor for signs of nifedipine toxicity
Anidulafungin	No significant interactions	(n/a)

^a Monitor pulmonary function tests (PFTs), thyroid stimulating hormone (TSH), and liver function tests (LFTs)

^b Theoretical interaction through the inhibition of hepatic CYP450 isoenzymes affecting cyclophosphamide metabolism and conditioning-related toxicities

medications (such as vomiting patients or those suffering significant mucositis). Dosage adjustments of posaconazole in patients with renal impairment or hepatic impairment are not required [74].

Posaconazole has demonstrated efficacy as prevention of IA and *Candida* infections in high-risk patients, most notably allogeneic SCT recipients [79] and neutropenic patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) [80]. In patients with neutropenia (AML or MDS), posaconazole reduced the number of proven or probable IAs compared to fluconazole/itraconazole (2% vs. 8%; $P < 0.001$) and improved survival ($P < 0.04$) [80]. For allogeneic SCT, recipients with graft versus host disease (GVHD), posaconazole was superior to

fluconazole in prevention of IA (2.4% vs. 7%; $P = 0.006$) and fungal deaths (1% vs. 4%; $P = 0.046$) [79]. In addition, studies have evaluated the efficacy of posaconazole for salvage treatment of IFDs caused by *Aspergillus* and *Zygomycetes* [75–77]. An open-label, multicenter study evaluating posaconazole as monotherapy for treatment of IA in patients who were refractory to or intolerant of conventional therapy reported an overall success rate of 42% (45/107) for subjects receiving posaconazole [75]. In a retrospective study of 91 patients with zygomycosis refractory to prior antifungal therapy, the authors reported that 60% of the subjects experienced a complete or partial response with posaconazole therapy [76]. Response rates reported in this study are similar to those reported

with AMB-D and lipid-based formulations of amphotericin B [12, 76].

From the available data, it appears that posaconazole is a promising alternative agent for the treatment of zygomycosis. While lipid-based formulations of amphotericin B is still considered by many to be the initial drug of choice for allogeneic SCT recipients with severe disease, it is likely that posaconazole will play a role in continued therapy for this serious disease. For instance, posaconazole may be used in sequence after polyene therapy. However, its use in combination with polyene remains uncertain. In vitro and animal models have not found posaconazole to add to polyene efficacy [81]. Also, since zygomycosis is so critically influenced by underlying disease and surgery, comparative studies will be difficult. For patients with IA refractory to or intolerant of amphotericin B, success rates have been comparable to other agents used for salvage therapy (such as echinocandins). It is important to note that there may not always be cross-resistance between azoles for *Aspergillus*, so relapse isolates with azole therapy should be checked for in vitro activity against both extended-spectrum azoles.

Tolerability of posaconazole appears to be comparable to fluconazole [79, 82]. The most common adverse events reported in clinical trials were gastrointestinal complaints and headache. Gastrointestinal complaints consist of nausea, vomiting, diarrhea, and abdominal pain, and occurred in up to 10% of patients in one clinical trial [83]. Other less-common treatment-related adverse events include elevation of liver enzymes and QT prolongation [79, 80, 83]. Of note, posaconazole does not have visual or skin adverse effects seen with voriconazole.

Posaconazole is not significantly metabolized by the CYP450 enzyme system. However, it is an inhibitor of the CYP450 3A4 isoenzyme [84]. Similar to voriconazole and other triazoles, interactions are expected (refer to Table 2) [74, 85–87]. However, in comparison to voriconazole, posaconazole appears to have fewer drug–drug interactions.

Significant interpatient variability of posaconazole serum concentrations can occur [68]. Therefore, similar to voriconazole, serum concentration monitoring of posaconazole is gaining clinical attention. The limited published data available suggest that there is a correlation between efficacy and enhanced drug exposure. Twenty-four percent of subjects (4/17) with IA responded with an average plasma

concentration (C_{avg}) and maximum plasma concentration (C_{max}) of 0.134 and 0.142 mg/l, respectively, compared to 75% (12/16) responding with C_{max} and C_{avg} of 1.48 and 1.25 mg/l, respectively [75]. Therefore, it may be reasonable to target a C_{max} of >1.48 mg/l or a C_{avg} of >1.25 mg/l after 5–7 days of therapy to ensure absorption and efficacy of drug in certain patient populations (patients failing therapy, patients on concomitant drugs that interact with posaconazole, or patients with poor oral absorption) [68, 75]. However, this is still an evolving issue which further warrants large, prospective studies to determine true clinical value of serum drug monitoring and specific drug level goals. In addition, like voriconazole, laboratories performing drug assay are limited.

Echinocandins

Three echinocandins are approved for clinical use: caspofungin, micafungin, and anidulafungin. They act by inhibiting the synthesis of β -1,3-D-glucan, an integral component of the fungal cell wall [14]. Decreased synthesis of β -1,3-D-glucan leads to destabilization of the fungal cell wall, cell lysis, and death [14]. Echinocandins demonstrate activity in vitro against *Candida* and *Aspergillus* spp., including those isolates that are resistant to azoles and amphotericin B. Echinocandins have limited or no in vitro activity against Zygomycetes and *Cryptococcus neoformans* [13, 14]. Although, there is some suggestion that Zygomycetes may be impacted with echinocandins in vivo [88]. Resistance to echinocandins among *Candida* spp. is rare, but reduced susceptibilities and specific mutational hot spots in the FKS1 gene have been reported in some *Candida* isolates, including the haploid, *C. glabrata* [89–91]. With further prolonged and frequent use of echinocandins, there will be a need to monitor direct resistance frequency because surely it will occur in some frequency and allogeneic SCT recipients might be a high-risk group to detect its occurrence.

All three echinocandins are available only in intravenous formulations and are dosed once daily. Loading doses are recommended with caspofungin (70 mg on day one followed by 50 mg/day) and anidulafungin (200 mg on day one followed by 100 mg/day) [92, 93]. Micafungin dosing is

100 mg/day for treatment of candidemia [94], 100–150 mg/day for treatment of IA [40], and 150 mg/day for esophageal candidiasis [94]. No dosage adjustments are required for anidulafungin or micafungin in patients with renal or hepatic impairment [93, 94]. However, dosage reduction of caspofungin is recommended for patients with moderate hepatic impairment (Child-Pugh score 7–9) [92].

All three echinocandins have demonstrated efficacy for the treatment of candidemia [37, 95–97]. A randomized double-blind study demonstrated the non-inferiority of caspofungin to AMB-D in non-neutropenic and neutropenic patients with invasive candidiasis [95]. Anidulafungin was shown to be non-inferior to fluconazole for the treatment of candidemia using a randomized, double-blind, non-inferiority trial design [96]. In fact, a successful outcome was experienced in 75.6% of patients treated with anidulafungin compared with 60.2% treated with fluconazole, and it met statistical criteria for superiority to fluconazole. However, when data from the site enrolling the most subjects were removed from the analysis, superiority of anidulafungin was not shown [96]. Finally, micafungin was shown to be non-inferior to both L-AMB and caspofungin in two separate randomized, non-inferiority studies [37, 97]. Micafungin at 100 and 150 mg/day were similar in successful outcome compared to 50 mg/day caspofungin [97]. Although, the majority of cases in most of these studies were non-neutropenic, it appears that neutropenic patients with candidiasis still have around a 60% success rate with echinocandins, which is about 10–20% less active, and this has importance to allogeneic SCT recipients [37, 95, 97]. Furthermore, their use in other forms of invasive candidiasis has been notable. For instance, in one study, seven out of eight patients with hepatosplenic were successfully managed with an echinocandin [98].

Due to their comparable clinical response, broad-spectrum of activity against *Candida* spp. and safety profile, we believe echinocandins are a more attractive option compared to amphotericin B formulations as initial treatment for invasive candidiasis (especially in patients with severe infections or those at increased risk of azole resistance) while awaiting speciation of the *Candida* spp. In cancer patients, they have been found to be cost-effective compared to L-AMB in the treatment of invasive candidiasis and candidemia [99]. In addition, echinocandins are

often used as alternatives to fluconazole in patients with severe infection and/or at highest risk of azole resistance [100].

Although not fungicidal *in vitro*, two echinocandins have demonstrated clinical efficacy against IA: caspofungin and micafungin [101–103]. In an open-label study of patients with proven or probable IA, 45% (37/83) of patients responded to caspofungin therapy [101]. Micafungin was evaluated as monotherapy or as combination therapy in patients with proven or probable IA who were either refractory or intolerant of first line-therapy [103]. Favorable responses were seen in 15 of 34 (44.1%) patients treated with monotherapy [103]. Due to their fungistatic nature, we generally do not recommend them as primary therapy for IA in allogeneic SCT recipients, but their use in combination and salvage therapy is frequently considered.

Echinocandins are generally well tolerated with very few adverse effects. Adverse events associated with therapy are infusion-related reactions and elevated liver enzymes. Infusion-related reactions have been reported more often with caspofungin (3–25%) compared with micafungin and anidulafungin (<2%) [104]. In order to minimize the potential for infusion-related reactions, infusions should be administered over a period of at least 1 h [105]. In addition to infusion-related reactions, elevated liver enzymes occur more frequently with caspofungin (1–15%) than with micafungin (1–8%) and anidulafungin (3–5%) [104]. Other treatment-related adverse events reported in clinical trials include fever, nausea, vomiting, and diarrhea [104]. Although not necessarily directly related, fever occurs up to 40% of patients treated with caspofungin and less frequently with micafungin and anidulafungin, while gastrointestinal effects occur in <7% of patients treated with any of the three echinocandins [104].

Echinocandins are not potent substrates, inhibitors, or inducers of enzymes of the CYP450 system [13]. Therefore drug–drug interactions are not frequent (refer to Table 2). Rifampin, phenytoin, carbamazepine, nelfinavir, efavirenz, and nevirapine may induce the clearance of caspofungin and therefore warrant increasing the dose of caspofungin to 70 mg/day [92]. In addition, interactions between caspofungin and immunosuppressants (such as cyclosporine and tacrolimus) have been confirmed [90]. However, further reports and case studies have shown that co-administration is generally well tolerated and the need of dose

adjustments of cyclosporine and tacrolimus are not common [106, 107]. It appears that micafungin and anidulafungin have fewer drug interactions compared with caspofungin. Micafungin increases plasma concentration levels of cyclosporine, sirolimus, and nifedipine [94, 108]. Currently, there are no known significant drug–drug interactions reported with anidulafungin [13]. In contrast to azoles, drug interactions are much less of an issue for echinocandins.

Combination Therapy

Poor rates of favorable treatment outcomes for severely immunosuppressed patients with serious IFDs (such as allogeneic SCT recipients), along with the potential to use different classes with distinct mechanism of actions, have sparked interest in use of combination antifungal therapy. However, with the exception of the clinical studies supporting the efficacy of combination therapy (AMB-D + flucytosine) for the treatment of cryptococcal meningitis [109–113], data from controlled clinical trials are generally lacking to support the routine use of combination therapy for other IFDs.

Combination therapy for candidemia has been evaluated in clinical trials [114, 115]. In adult patients without neutropenia assigned randomly to either combination therapy of AMB-D and fluconazole or fluconazole monotherapy, the combination resulted in a trend for better overall success rates [114]. However, differences between groups were not statistically significant (69% vs. 56%; $P = 0.08$). Also, there was some bias toward entry of sicker patients in the monotherapy group, but it did not show any antagonism between polyene and azole for invasive candidiasis.

Currently, the greatest attention has been placed on combination therapy for invasive mold infections. Evidence for combination therapy in IA and Zygomycetes is mainly limited to retrospective analyses and prospective, non-comparative studies [76, 103, 116–120]. Studies for treatment of IA have shown better survival rates for combination therapy compared to historical controls [116, 118, 120]. In addition, a recent randomized study with low statistical power comparing L-AMB plus caspofungin to L-AMB monotherapy in immunocompromised patients showed a more favorable response for combination therapy (67% vs. 27%; $P = 0.028$) [120]. In an open-label (non-

randomized) study evaluating posaconazole in patients with proven or probable zygomycosis, 13 of 91 patients received combination therapy of posaconazole and lipid-based formulations of amphotericin B. Partial response occurred in 46% of the 13 patients, while 31% experienced failure [76]. Finally in a retrospective study of 41 patients, superior success was noted with ABLC plus caspofungin compared to those receiving ABLC monotherapy (100% vs. 45%; $P = 0.019$) [88]. However, current data for IFDs due to molds are limited and do not support the routine use of combination therapy. Until data from large, well-controlled studies are available, the clinical benefits of combination therapy for mold infections will remain uncertain and practiced without robust guidelines. Therefore, combination therapy becomes a bedside decision weighing the risks versus benefits in an individual allogeneic SCT recipient without precise knowledge of either. That said, failure is high for mold disease in allogeneic SCT recipients and combination therapy should not necessarily be avoided if a high burden of organisms needs to be reduced.

Conclusions

IFDs continue to cause significant morbidity and mortality in allogeneic SCT recipients. New antifungal agents have been developed and added to our formulary over the last decade to improve management options for these infections. Lipid-based formulations of amphotericin B provide clinicians with an effective and less nephrotoxic alternative to AMB-D. However, amphotericin B formulations have become second-line therapy for treatment of IA and most invasive candidiasis infections. Yet, it still remains the initial drug in the treatment of zygomycosis. Voriconazole and posaconazole offer extended spectrums of antifungal activity against *Aspergillus* spp. and Zygomycetes (posaconazole only) compared to fluconazole. Voriconazole has replaced amphotericin B as primary therapy for IA, while posaconazole appears to be a promising alternative agent for treatment of zygomycosis. In addition, the echinocandins provide agents that are effective against *Candida*, well tolerated, and have minimal drug interactions, and for those reasons, are considered the first-line agents for initial therapy for invasive candidiasis in patients with severe infections and/or those at increased risk of azole resistance.

However, therapeutic problems do exist among these newer agents, specifically adverse drug events (mainly voriconazole), drug–drug interactions associated with the triazoles, and lack of alternative preparations (e.g., intravenous preparations of posaconazole and oral preparations for the echinocandins). Furthermore, the role of therapeutic drug monitoring with posaconazole and voriconazole, as well as combination therapy, are still unclear and warrant further evaluation.

A final word on antifungal agents in the allogeneic SCT patient population is extremely important. The appearance of new agents in three separate antifungal classes is outstanding and the clinician has excellent choices for prevention and treatment of the dreaded IFDs in these fragile patients. However, the allogeneic SCT patient is frequently trapped between two major forces—too little immunity or too much. It is the “Goldilock’s” paradigm of immunity (not too much or not too little), but the immunity must be just right to clear these infections [121]. Therefore, every attempt must be made to improve the poor immune status of the host (cytokine administration, cell transfusions, nutrition, and control of underlying disease). However in the process, many of our reported failures may be due to an overzealous return of immune cells producing the immune reconstitution inflammatory syndrome with its enlarging radiographic lesions, acute respiratory distress syndrome, or fever. It is therefore important that we carefully monitor cultures, biomarkers (such as β -glucan and galactomannan), histopathology, and patient’s well-being to help truly assess the curative ability of our outstanding antifungal agents in the allogeneic SCT patient.

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