Medical Mycology September 2006, **44**, S357–S362

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Treatment of invasive aspergillosis: Polyenes, echinocandins, or azoles?

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Three classes of antifungals – the polyenes, the echinocandins, and the extended spectrum azoles – are now available for treating invasive aspergillosis (IA). New agents and formulations in these classes offer the possibility of decreased toxicity and improved outcomes. With the availability of newer antifungals, clinicians are challenged to understand the advantages and limitations of these new choices. Standard amphotericin B deoxycholate is associated with poor outcomes in addition to unacceptable toxicity and is no longer recommended as primary therapy for most patients. Lipid formulations of amphotericin reduce toxicity, but because of cost and toxicity concerns, they may not be used at optimal doses. Interestingly, a recent trial showed that initial use of higher doses of liposomal amphotericin at 10 mg kg^{-1} d^{-1} did not improve efficacy and was associated with more toxicity. Due to lack of complete killing or inhibition of *Aspergillus*, the echinocandins are not frequently used as primary therapy for aspergillosis, although their minimal toxicity and potential for combination therapy remains attractive. The newer triazoles, including voriconazole and posaconazole, offer fungicidal activity against *Aspergillus* and, for voriconazole, both intravenous as well as oral therapy. Voriconazole was compared with amphotericin B followed by other licensed therapy in a global trial that showed better outcomes and improved survival so that voriconazole is recommended as primary therapy for most patients with this disease. These studies also show that early, effective therapy is a key factor for a successful outcome. Consideration of risk for IA and early initiation of therapy may improve outcomes in this often lethal infection.

Keywords aspergillosis, polyenes, echinocandins, extended spectrum azoles

Introduction

Invasive aspergillosis (IA) remains an important cause of morbidity and mortality in immunosuppressed patients [1,2]. Early, effective antifungal therapy is critical in improving patient outcomes in IA. Unfortunately, the diagnosis of infection is difficult and treatment with amphotericin B deoxycholate, which had been the previous 'gold standard' therapy for this disease for more than four decades, is often ineffective and associated with unacceptable toxicities [3]. Patients with extensive infection and those with disseminated disease have poorer outcomes even with aggressive antifungal therapy. Thus, in patients with IA, strategies that utilize primary therapy with amphotericin B deoxycholate can no longer be recommended due to its substantial toxicity and limited efficacy. Moreover, outcomes of salvage therapy following progression of infection or due to toxicity following amphotericin B are extremely limited [4].

New antifungals have been developed to target *Aspergillus*. Three classes of antifungals are now available for treating these often lethal infections, the polyenes, including lipid formulations of amphotericin B, the echinocandins, and the newer azoles [5]. With these antifungal options, it is imperative that clinicians

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DOI: 10.1080/13693780600826715

Table 1 Antifungal agents with activity against *Aspergillus* species

Class	Agents	Advantages and limitations
Polyene	Amphotericin B deoxycholate (AmB)	Efficacy limited; substantial toxicity associated with increased mortality and increased hospital costs; potential decreased toxicity with continuous infusions [3,6,7,18]
	Lipid formulations of amphotericin B: L-AmB, ABLC, ABCD	Less toxicity than AmB; systemic toxicities: ABCD >> ABLC > L-AmB; higher doses anecdotally more effective; cost significant barrier to extensive use [13,16,46,47]
Triazole	Itraconazole	Indicated for second-line therapy and sequential oral therapy; suspension improves bioavailability; limited efficacy data for intravenous form; renal/liver toxicity from chemotherapy interactions; liver, gastrointestinal toxicity [2,30,48]
	Voriconazole	Recommended primary therapy for most patients due to survival advantage vs AmB; drug interactions; visual, liver, skin toxicities [32,34]
	Posaconzole	Evaluated as salvage therapy of aspergillosis and prophylaxis; oral suspension only; well-tolerated in clinical trials [38]
Echinocandin	Caspofungin, micafungin, anidulafungin	Salvage and combination therapy; regulatory approval only for caspofungin; well-tolerated; potential cyclosporine interaction for caspofungin [20,24,25,29]

appreciate the advantages and limitations of these drug classes in order to optimally mange patients with this infection (Table 1). In this review, several key questions regarding the use of these agents in IA will be addressed: (i) why have outcomes been so poor; (ii) what is the real impact of an early diagnosis; (iii) what are current options for therapy; and (iv) can management strategies using these new agents improve outcomes in our patients?

Polyenes

Amphotericin B has long been considered standard therapy for serious fungal infections including IA. However, multiple studies have now established not only the unacceptable toxicity of this compound for serious infection but also demonstrate its lack of efficacy in high-risk patients with these infections [3,6]. Bates and colleagues assessed overall mortality and costs of acute renal failure in 707 adult patients receiving amphotericin B deoxycholate [7]. In that study 30% of patients developed acute renal failure which was associated with significantly higher mortality rates (54% vs. 16% mortality in patients who did not develop renal toxicity). In addition, those patients with acute renal failure had an increased length of hospital stay of 8.2 days which resulted in an increased mean hospital cost of US$29 823. Thus, this study provided strong evidence that utilization of an inexpensive drug in terms of acquisition costs not only resulted in higher healthcare expenditures but also dramatically poorer outcomes.

Another limitation of polyene therapy that is not always considered is that of antifungal resistance, which is particularly more common in *Aspergillus* spp. other than *A. fumigatus* [8]. Sutton and colleagues reported that of 918 *Aspergillus* spp. received by a reference laboratory for susceptibility testing, only 57% were *A. fumigatus,* followed by *A. flavus* (12%), *A. terreus* (12%), and others [9]. Polyene resistance in *A. terreus* is now well recognized and, as might have been anticipated, minimum inhibitory concentrations (MICs) for amphotericin B were ≥ 2 μg/ml in 90% of those isolates. In addition, and perhaps surprisingly, MICs ≥ 2 μg/ml were also found in 51% of *A. flavus* isolates and 50% for *A. ustus*, an uncommon but highly resistant organism. Notably, the minimum fungicidal concentrations (MFCs) for amphotericin B were ≥ 16 μg/ml in 24% of the *A. fumigatus* tested. Based on those results, this author would speculate that poor outcomes may be not only due to toxicity of amphotericin B but may also be due in part to unsuspected antifungal resistance in some *Aspergillus* strains or species.

Lipid formulations significantly reduce the toxicity associated with amphotericin B and have been studied most extensively for empirical use in febrile neutropenia [10]. Because of cost and toxicity concerns these agents may not be used initially in doses that prevent breakthrough of aspergillosis or effectively treat established

infection, although comparative data to support the optimal dose of these agents is not established [11,12]. While there are few prospective, comparative data in established IA to support their use for primary therapy [13,14], historical reviews have suggested the utility of lipid formulations of amphotericin B, particularly when used in higher doses [15,16]. A recent trial showed that initial use of higher doses of liposomal amphotericin B at 10 mg kg^{-1} d^{-1} did not improve efficacy and was associated with more toxicity than lower doses, suggesting that the routine use of very high doses may not be routinely warranted [17].

Another approach to decrease toxicity associated with amphotericin B deoxycholate is the use of continuous drug infusions. In an open, observational study conducted mostly in patients with suspected rather than documented fungal infections, Imhoff and colleagues reported that doses of amphotericin B deoxycholate could be safely increased to 2 mg kg^{-1} d^{-1} with infusion reactions occurring in 18% and more than twofold increases in creatinine occurring in only 16%. Dose-limiting toxicity in that study occurred in only one of 33 patients [18]. A major concern of utilizing this approach is the fact that data in animal models show peak serum level/MIC is the best pharmacokinetic predictor of outcome in animal models of infection so that efficacy may be reduced in those patients with documented infection due to lower peak serum levels that the modest increase in tolerability is unable to overcome [19].

Echinocandins

The echinocandins are a novel class of antifungal with activity against most species of *Aspergillus* [20]. These agents, which include caspofungin, micafungin and anidulafungin, lack of complete killing or inhibition against *Aspergillus* with activity focused on the growing hyphal segments [21]. For that reason, these agents have mostly been used and evaluated for salvage therapy of IA or in combination with other agents [22]. Although all these agents have *in vitro* activity, only caspofungin has received regulatory approval for that indication [5]. The intravenous delivery of these agents, combined with their minimal toxicity and few drug interactions make them ideal candidates for combination therapy. Both *in vitro* studies and *in vivo* animal models show significant synergistic activity with the echinocandins, particularly in combination with the newer azoles [23–25]. Clinical evidence regarding combination therapy has been limited to anecdotal reports and historical comparisons [26–28], but the use of voriconazole combined with caspofungin was reported by Marr and colleagues to significantly improve survival as compared with voriconazole alone when used following initial polyene therapy [29]. Prospective clinical studies are urgently needed to establish the utility of combination therapy for this disease.

Triazoles

Although itraconazole has activity against *Aspergillus*, its clinical utility for seriously ill patients with invasive mycoses including IA has been limited by drug interactions and toxicity as well as erratic bioavailability of the oral suspension [30]. The newer triazoles, including voriconazole and posaconazole, offer the potential advantage of fungicidal activity against *Aspergillus* and – for voriconazole – both intravenous as well as highly bioavailable oral therapy [31]. The efficacy of voriconazole as compared with amphotericin B deoxycholate followed by other licensed therapy in a global clinical trial showed better outcomes and improved survival of initial voriconazole therapy so that voriconazole is now recommended as primary therapy for most patients with this disease [32,33]. In addition, voriconazole has also been successfully used in patients with disseminated infection and in those with central nervous system infection, which has previously been considered a near fatal diagnosis [34,35]. Voriconazole also has *in vitro* and clinical activity against infection due to *A. terreus* which is commonly resistant to polyene therapy [8]. Even with these favorable outcomes, there are several important considerations in utilizing voriconazole therapy, including the potential for drug interactions, adverse events such as potentially dose-limiting hepatic toxicities as well as frequent visual and skin toxicities which are less likely to require discontinuation of therapy. Other considerations with the use of voriconazole include its lack of activity against Zygomycetes, cross-resistance with other azoles against yeasts and the accumulation of the cyclodextrin vehicle of the intravenous formulation in renal insufficiency [5,36]. A major advantage of voriconazole is the availability of both an intravenous and oral formulation so that step-down therapy can be utilized. However, it is important to recognize that some patients may have inadequate levels of oral drug particularly if a standard 200 mg twice-daily dosage is used rather than the indicated 3 mg/kg twice-daily dose which has been studied for the intravenous formulation [37]. In patients with inadequate responses or in whom drug toxicity is suspected, some experts recommend measurement of voriconazole levels, although this is not routinely recommended or needed. In our experience, dosing of

the oral formulation on a weight basis has produced satisfactory results with good tolerability.

Posaconazole, another of the extended spectrum azoles, has recently received regulatory approval in the European Union and has been shown to have activity in the salvage setting for treatment of IA [38]. In addition, posaconazole has also been shown to be effective in high-risk patients as prophylaxis against invasive mycoses including *Aspergillus* with reduction in breakthrough mould infections, including aspergillosis and improved survival [39,40]. A limitation for the use of posaconazole in acute disease is the current lack of a clinically available intravenous formulation, although tolerability of the suspension in clinical trials has been favorable and an intravenous preparation is undergoing clinical development [38].

Early diagnosis

The importance of early, effective antifungal therapy was seen in the global trial comparing voriconazole to amphotericin B deoxycholate [4,32]. In that study, successful outcomes of rescue therapy following initial amphotericin B occurred in only 21% of patients with progressive infection [4]. Outcomes were even further improved when voriconazole was begun at early suspicion of the diagnosis – that is computed-tomography (CT) evidence of infection in high-risk patients – with responses of 67% as compared to only 19% responses with initial amphotericin B deoxycholate utilizing a mycologically proven diagnosis [4,32].

Non-culture-based diagnostics combined with early computed tomography will potentially further increase the likelihood of an early diagnosis, so that the strategy of combining non-culture-based methods along with clinical and radiographic evidence of infection could allow prompt initiation of effective *Aspergillus* therapy [41,42]. Currently detection of both glactomannan and β-D-glucan are commercially available for the diagnosis of IA, the latter being a non-specific diagnosis of a variety of invasive mycoses [43,44]. Although significant advances have been made in polymerase chain reaction (PCR) techniques, these assays remain investigational due to the fact that current methods have not been externally validated and do not utilize standardized methods or reagents [42,45].

Conclusions

Early, effective therapy is a key factor for a successful outcome of IA in high-risk patients. Careful consideration of risk for IA and early initiation of therapy in those patients may improve outcomes of patients with this often lethal infection. The availability of newer antifungal agents in three drug classes, the polyenes, the echinocandins and extended spectrum triazoles, offer significant improvement in activity and tolerability so that better outcomes can be achieved in patients with this often lethal infection.

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