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Review

Treatment of *Aspergillus terreus* infections: A clinical problem not yet resolved

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ABSTRACT

Despite the use of recommended therapies, invasive infections by *Aspergillus terreus* show a poor response. For years, investigative studies on the failure of therapy of fungal infections have focused on in vitro susceptibility data. However, it is well known that low minimum inhibitory concentrations (MICs) are not always predictive of response to therapy despite a correct dosage schedule. Many experimental and clinical studies have tried to establish a relationship between MICs and outcome in serious fungal infections but have come to contradictory and even surprising conclusions. The success or failure of treatment is determined by many factors, including the in vitro susceptibility of the causative fungal isolate, the pharmacokinetics/pharmacodynamics of the drug used for treatment, pharmacokinetic variability in the population, and the underlying disease that patients suffer. To try to understand this poor response to treatment, available data on the in vitro susceptibility of *A. terreus*, the experimental and clinical response to amphotericin B, triazoles and echinocandins, and the pharmacokinetics/pharmacodynamics of these antifungals have been reviewed. Of special interest are the fungistatic activites of these drugs against *A. terreus* and the high interpatient variability of serum drug levels observed in therapy based on triazoles, which make monitoring of infected patients necessary.

1. Introduction

Aspergillosis is the most prevalent mould infection in immunocompromised patients. Clinical data suggest that the innate immune response is able to clear aspergilli from the entry portal despite continuous exposure to conidia [1]. However, patients with impaired cell-mediated immunity are at risk of acquiring invasive aspergillosis (IA) [1]. *Aspergillus fumigatus* is the most common agent of IA, but the incidence of other species such as *Aspergillus terreus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus nidulans* and *Aspergillus calidoustus* has increased in recent years [1–4].

Treatment of IA is complex because of the diversity of species with different antifungal susceptibilities able to cause infections and especially because of the underlying illnesses that most patients suffer. Voriconazole is the recommended drug for treating IA, and lipid formulations of amphotericin B (AmB) or micafungin are alternative therapies [5]. However, despite the use of antifungal treatments, the outcome of IA is often discouraging, with high rates of mortality ranging from 27% to 80% [6]. Numerous studies have been carried out in an attempt to establish the clinical breakpoints (CBPs) for susceptibility and resistance of *Aspergillus* to AmB, azoles and echinocandins. Whilst the Clinical and Laboratory Standards Institute (CLSI) has not proposed CBPs for any antifungal against moulds, the Subcommittee on Antifungal Susceptibility Testing (AFST) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has recently established CBPs for AmB, itraconazole, voriconazole and posaconazole against some *Aspergillus* spp. [7]. In recent years, numerous clinical isolates with acquired resistance to the abovementioned drugs have been described and, in an attempt to detect them, the CLSI and the EUCAST–AFTS have established corresponding epidemiological cut-off values, called ECVs [8] or ECOFFs, respectively [7], for the different drug/species combinations. The ECV is the highest susceptibility endpoint in a species subpopulation that includes isolates with no detectable acquired resistance mechanisms, known as wild-type (WT) isolates [9]. In the absence of established CBPs, ECVs for antifungal drug/*Aspergillus* spp. combinations have been proposed to identify strains with acquired mechanisms of resistance to AmB, azoles and echinocandins (non-WT) [8,10–13]; however, their clinical significance is not yet well understood.

Aspergillus terreus is an emerging opportunistic fungus whose clinical incidence has increased in recent years [14]. Of special concern is the high mortality of invasive infections caused by this species. Its treatment commonly fails and its incidence is

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Table 1
Reported invasive aspergillosis (IA) by *Aspergillus terreus*: risk factors and mortality*.

Type of IA (*n*)	Haematological malignancy [*n* (%)]	Neutropenia [*n* (%)]	Mortality (%)
Pulmonary (46)	29 (63.0)	20 (43.5)	87
Cardiovascular (14)	2 (14.3)	1 (7.1)	100
Disseminated (15)	11 (73.3)	5 (33.3)	99
Others (15)[a]	1 (6.7)	0 (0)	33

[a] Included central nervous system, peritoneal, hepatic and osteoarticular localisations.
* Data obtained from retrospective clinical trials and individual case reports.

increasing, making it essential to revise therapies [10]. Invasive infections by this species constitute nearly 4% of all IA [14] and the mortality rates are higher than for other species of *Aspergillus* [15,16]. Clinical interest in *A. terreus* infections lies in their lack of response to AmB and the relatively high percentage of clinical isolates with acquired resistance to azoles, particularly to voriconazole. Table 1 shows the types of IA caused by this species, underlying diseases, risk factors and mortality rates of reported cases. The data in Table 1 were obtained from retrospective clinical trials and individual case reports. We have reviewed the available data on in vitro susceptibility as well as the experimental and clinical pharmacokinetic/pharmacodynamic (PK/PD) profiles of the recommended antifungal drugs used in the treatment of *A. terreus* infections, which might explain the difficulties encountered in the management of these complex mycoses.

2. Antifungal therapy

2.1. Amphotericin B

Aspergillus terreus is intrinsically resistant to AmB; however, the basis for this resistance is poorly known, although the higher level of catalase production by this species in comparison with *A. fumigatus* could explain its resistance by blocking the oxidative damage produced by AmB [17,18]. Data on in vitro susceptibility of *A. terreus* are shown in Table 2. Minimum inhibitory concentrations (MICs) of this drug are generally ≥2 mg/L [6,15,16,20–46], although very low MICs (0.06–0.125 mg/L) have also been reported [47,48]. The CLSI and EUCAST have categorised *A. terreus* as resistant to AmB and have established an ECV and ECOFF of 4 mg/L, with the percentage of non-WT isolates being 3.9% [11]. Interestingly, and different to other *Aspergillus* species such as *A. fumigatus* or *A. flavus*, nearly 70% of *A. terreus* isolates tested show differences of more than 2 dilutions between the MICs and the minimum fungicidal concentrations (MFCs) [24,27]. This could explain the reported in vitro fungistatic effect of AmB against this fungus [40] and its poor efficacy against *A. terreus* infections. As this fungus affects mainly neutropenic patients, the significance of such fungistatic activity on their defective innate immunity is unknown, as no evidence exists of the importance of fungicidal or fungistatic activity in IA patients [49].

Animal studies have confirmed the resistance of *A. terreus* infections even to high doses of amphotericin B deoxycholate (AmBD) or its liposomal formulation in murine and rabbit models [36–39,50–52]. However, a recent experimental study in neutropenic mice suggested that *A. terreus* might be susceptible to high doses of liposomal amphotericin B (L-AmB), which would allow high concentrations of the drug to be achieved in lungs (4–8 mg/L) [53] (Table 3).

In the clinical setting, retrospective studies on IA by *A. terreus* have revealed high rates (80–90%) of treatment failure with AmBD [16,54–56], which decreased to 64% when L-AmB was used as the primary therapy [16]. Some studies have tried to establish a correlation between AmB MICs and patient outcome and have reported contradictory results. MICs ≥2 mg/L were linked to fatal outcomes in a study of nine patients who were infected by *A. terreus* and treated with AmB, all of whom died [21]. However, there were important limitations of that study, such as the criterion for the MIC endpoint (≥75% growth inhibition), the small sample size and the lack of those infected with strains with AmB MICs <2 mg/L. Surprisingly, in a recent study that included 13 patients, the mortality rate after 6 weeks for those infected with isolates with MICs ≤1 mg/L was 75%, whilst when infected with strains with MICs >1 mg/L it was only 22% [42]. Although the sample size was low, these results are difficult to understand and would seem to demonstrate the poor predictive value of MICs in these infections. A study on the pharmacokinetics of AmB showed the small variability of peak serum levels (C_{max}) in healthy volunteers, with mean values of 1.43 ± 0.2 mg/L [57]. These data cannot explain the discrepancies between MICs and outcome cited above [21,42]. Other factors such as correction of neutropenia, surgery or drug dosage may be more important for the outcome of the infection [21,42]. A high variability in peak plasma levels of 2.83 ± 1.17 mg/L in neutropenic patients treated with AmB at 1 mg/kg/day has been reported [58]. Similarly, peak plasma levels of 0.51 ± 0.28 mg/L have been achieved in critically ill patients who received lower doses of AmB [59]. Pharmacokinetics might explain, in part, the differences between the patient response to AmB and to L-AmB treatments. The C_{max} reached in five healthy volunteers who received AmBD at 0.6 mg/kg was near to 1.5 mg/L, whilst in another five who received the lipid formulation at 2 mg/kg the C_{max} was ca. 15 times higher (22.9 ± 10 mg/L) [57]. In animal models, the PD parameter that is predictive of efficacy for AmB considering a concentration-dependent killing activity for this drug is the C_{max}/MIC, with ratios of 4 and 10 being considered predictive of 50% efficacy and maximal efficacy, respectively [60]. Although data on AmB/*A. terreus* pharmacodynamics in humans are not available, high C_{max}/MIC ratios are more easily achieved with L-AmB on the basis of the higher C_{max} achieved with this formulation. However, the PK interpatient variability for L-AmB is higher than for AmBD, therefore sufficient serum levels are not reached in some patients with the liposomal formulation [57,61]. This fact might explain in part why the survival rate (36%) is better in patients treated with L-AmB than in those treated with the deoxycholate formulation (10–20%), although the differences in survival are not remarkable, probably due to the host factors cited above. On the other hand, data on experimental pharmacokinetics/pharmacodynamics in an in vitro dynamic model have demonstrated that higher blood concentrations of AmB are required to achieve efficacy against *A. terreus* than against *A. fumigatus* strains with the same MICs [62,63]. On the basis of the PK/PD data obtained with this in vitro dynamic model, breakpoints of ≤0.25 mg/L and ≥1 mg/L for susceptibility and resistance, respectively, have been proposed recently for AmB against *A. terreus*, with those proposed for *A. fumigatus* being one dilution higher [64]. This is probably due to the fungistatic activity of AmB against *A. terreus*, since the predictive C_{max}/MIC for efficacy is established while taking into account the drug concentration-dependent killing activity rather than the fungistatic activity [60]. All these data appear to be the origin of the difficulty and unpredictable results of treatment with AmB of IA by *A. terreus*.

2.2. Itraconazole

Itraconazole also shows a fungistatic effect against *A. terreus* [24], with MICs ranging from 0.07 mg/L to 2 mg/L [6,15,22,24,25,27,29–36,38,41–43,45,50,65–69] (Table 2). The CBPs proposed by EUCAST for this drug are ≤1 mg/L for susceptibility and >2 mg/L for resistance. The CLSI and EUCAST proposed an ECV of 1 mg/L and an ECOFF of 0.5 mg/L, respectively, for the itraconazole/*A. terreus* combination [10]. On the basis of the CLSI criterion, only WT isolates have been described for this antifungal/species