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Treatment of Non-*Aspergillus* Mold Infections: a Focus on Mucormycosis and Fusariosis

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Abstract

Purpose of review Mucormycosis and fusariosis are associated with severe morbidity and high fatality rate. This review will discuss the challenges associated with the treatment of mucormycosis and fusariosis with a focus on recent data on antifungal susceptibility, novel therapeutic modalities, and combination therapy. Overall, the review aims to provide guidance to optimize management of these difficult-to-treat infections.
Recent findings Isavuconazole has comparable efficacy with liposomal amphotericin B for the treatment of mucormycosis. Treatment of fusariosis remains challenging, but voriconazole has been associated with improved outcome. Posaconazole has successfully been used as salvage therapy for both infections. Combination therapy is increasingly used although robust data supporting its efficacy is limited.
Summary The first-line therapy for mucormycosis remains liposomal amphotericin B with posaconazole and isavuconazole being acceptable alternatives. Fusariosis should be treated with either voriconazole or liposomal amphotericin B. Combination therapy may have a role although its clinical benefit remains uncertain.

Introduction

Non-*Aspergillus* molds are emerging pathogens in immunocompromised patients. Data from the Transplant-Associated Infection Surveillance Network (TRANSNET) have reported that mucormycosis accounted for 9% and 2.1% of all invasive fungal infections (IFIs) in hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients, respectively [1, 2]. Fusariosis accounted for 3% of IFIs in HSCT recipients [1]. While uncommon, these emerging fungi are of concern due to their aggressive course and high fatality rate. This article reviews the recent literature on the management of infections caused by Mucorales and *Fusarium*.

Invasive Mucormycosis

Mucorales are the most common non-*Aspergillus* molds and cause mucormycosis, a serious and life-threatening disease. *Rhizopus* is the most common species associated with human disease, followed *by Mucor*, *Rhizomucor*, and *Leichtheimia* [3–6]. The incidence of mucormycosis is estimated at 0.43–1.2 cases per million population per year [7]. The disease usually occurs in immunocompromised hosts such as patients with hematologic malignancy or HSCT and SOT recipients which represent 29–57% of patients with mucormycosis [3, 6]. Patients with uncontrolled diabetes represent 17–36% of cases [3, 6]. Clinical syndromes vary by underlying conditions: rhinocerebral disease being the most common manifestation in diabetic patients whereas pulmonary disease is more commonly observed in transplant recipients [8]. Mortality associated with mucormycosis is around 40–50% [6,9]. An increasingly recognized at-risk group is immunocompetent individuals who develop rapidly progressive skin and muscle necrosis after trauma such as tornado, combat-related wound, tattoo or intradermal injection, or catheter insertion [10]. *Apophysomyces* and *Saksenae* are associated with severe necrotizing fasciitis, and the majority of cases have been reported from India, Australia, and the USA [11–13]. The mortality in this latter group is lower (24–30%).

Mucormycosis is traditionally diagnosed by culture or histopathology [14]. Mucorales are recognized by their broad, sparsely septate, ribbon-like hyphae. Mucorales typically lack beta-D-glucan and galactomannan from their cell wall, and thus, these markers are not detected in mucormycosis [14]. Molecular diagnosis is increasingly used in clinical practice to improve diagnostic yield [15]. Currently, there are no validated minimum inhibitory concentration (MIC) breakpoints for any antifungals. While antifungal susceptibility testing need not be performed routinely, they may provide guidance for treatment in selected cases.

The cornerstone of therapy in mucormycosis consists of three important modalities: early antifungal therapy, adequate surgery, and reversal of immunosuppression. Adjunctive therapy may also be considered in refractory or severe cases.

Early antifungal therapy

Early administration of antifungal agent is a crucial step in the management of mucormycosis. A delay in antifungal therapy for more than 5 days after

diagnosis is associated with a twofold increase mortality risk at 90 days [16]. Among all systemic antifungal agents currently used in clinical practice, polyenes and triazoles are the most efficacious antifungal agents active against Mucorales species.

Polyenes

Amphotericin B deoxycholate (AmBd) has the most favorable in vitro activity against Mucorales [17]. Most Mucorales species demonstrate low MIC to AmB; however, some species such as *Cunninghamella* have higher MIC [17]. Historically, the standard treatment for mucormycosis consisted of AmBd [3]. Nevertheless, the use of AmBd is associated with an unacceptably high nephrotoxicity rate. Liposomal amphotericin B (LAmB) is associated with a similar outcome but lower nephrotoxicity [3, 18, 19]. In a non-comparative retrospective multicenter study, LAmB for treatment of mucormycosis was associated with 32% successful outcome and 39% survival [20]. One retrospective study even suggested improved survival among patients receiving LAmB compared with AmBd (62% vs. 39%, respectively) [21]. LAmB was also an independent factor for survival in a retrospective study of SOT recipients with rhinocerebral mucormycosis [22]. As such, LAmB is favored over AmBd for treatment of mucormycosis [23].

The optimal dosage of LAmB remains uncertain, but a higher dosage has been associated with better efficacy and is recommended by many guidelines [24, 25]. Data from the Fungiscope registry showed favorable clinical outcome with a median dose of 5 mg/kg/day; however, there was no comparative group [26]. Animal studies demonstrated that higher LAmB dose (10 mg/kg/day) resulted in more effective fungal clearance compared with 5 and 1 mg/kg/day [27]. A pharmacokinetic study comparing various LAmB dosage regimens (7.5, 10, 12.5, and 15 mg/kg/day) found optimal AUC measurements with dose of 10 mg/kg/day [28]. These pre-clinical results led to a prospective pilot study (AmbiZygo) to evaluate the efficacy and tolerability of high dose (10 mg/kg/day) of LAmB combined with surgery for treatment of 34 patients with mucormycosis. At 12 weeks, favorable response was observed in 45% which was comparable with clinical outcome observed in the Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT) study (40%) where lower dose of LAmB was used (7.5 mg/kg/day) [29, 30]. However, high-dose LAmB was associated with high rates of nephrotoxicity (40%). As such, the routine use of LAmB at 10 mg/kg/day for the treatment of mucormycosis is not recommended but may be considered for central nervous system infection [24].

Triazoles

Among azoles, only isavuconazole and posaconazole are active against Mucorales [17, 31]. Isavuconazole has good in vitro activity against Mucorales isolates with the exception of *Mucor circinelloides* [32, 33]. The Isavuconazole treatment for mucormycosis (VITAL) study was a recent phase III, open-label, non-comparative trial assessing the efficacy and safety of isavuconazole (200 mg/day for 180 days or until disease resolution) for treatment of mucormycosis [34••]. Among the 37 patients with invasive mucormycosis, the mortality rate at day 42 was 37.8%. Twenty-one patients received isavuconazole as primary

therapy while 16 patients were treated disease refractory to standard therapy (salvage). The former group was compared with 33 matched case-control patients treated with AmBd from the FungiScope registry [34••]. The mortality rate was similar between cases and controls (33.3 vs. 41.3%, respectively). In this study, the most common side effects were gastrointestinal complaints, such as nausea, vomiting, and diarrhea. Given the good safety profile and availability in both oral and intravenous forms, isavuconazole is an attractive alternative to LAmB [35]. In addition, isavuconazole has several advantages over other azoles such as fewer drug interaction with calcineurin inhibitors [36], shortening rather than lengthening of the QT interval [37], bioavailability unaffected by mucositis [38], unaltered pharmacokinetic in the setting of hepatic or renal impairment [39], and lack of need for therapeutic drug monitoring [40]. Following the VITAL study, the Food and Drug Agency licensed isavuconazole for the treatment of mucormycosis, while the European Medicine Agency licensed isavuconazole to those for whom AmB is deemed inappropriate. In one cost-effectiveness study conducted in the UK, isavuconazole was cost-effective compared with LAmB followed by oral posaconazole [41]. Nevertheless, clinical experience with isavuconazole for primary treatment of mucormycosis remains limited [35, 42–44]. As such, the place of isavuconazole has not yet been specified in the most recent guidelines.

Posaconazole is also active against Mucorales species. Clinical studies on the use of posaconazole in mucormycosis are limited to salvage therapy, with a reported efficacy ranging from 50 to 79% [45–47]. There are no data to support the use of posaconazole as first-line therapy; therefore, its use should be reserved for salvage treatment only. Most studies were conducted with oral suspension formulation of posaconazole which was limited in terms of bioavailability and food-drug and drug-drug interactions. The clinical efficacy of the sustained release tablet formulation (which has theoretically improved bioavailability and pharmacokinetic profile) and of the intravenous form has not been studied extensively [48].

Combination therapy

Given the high fatality rate associated with monotherapy for mucormycosis, combination therapy is an attractive option. The rationale for using combination therapy is the potential synergistic effect of multiantifungal agents which may lead to improved outcome compared with monotherapy.

The combination of polyene with an echinocandin has been the most studied. Traditionally, echinocandins are considered ineffective against Mucorales, although *Rhizopus oryzae* expresses the target enzyme for echinocandins (1,3-beta-D-glucan synthase) [49]. Interestingly, the combination of LAmB and echinocandin demonstrated synergistic effect and improved survival in neutropenic or diabetic ketoacidotic mice with *Rhizopus oryzae*–invasive infection [49–51]. One retrospective study of 41 patients with rhinocerebral mucormycosis showed that combination therapy of LAmB with echinocandin resulted in greater success rate (100 vs. 45%; $P = 0.02$) and survival benefit compared with LAmB monotherapy [52].

The combination of polyene and azole has also been studied. In animal studies, the combination of LAmB and posaconazole yielded conflicting results [53, 54]. There are few clinical studies on the use of combination of LamB and

posaconazole. In a prospective observational study of 50 SOT recipients with mucormycosis, five patients were treated with LAmB combined to posaconazole and had lower success rate compared with those who received LAmB monotherapy (40% vs. 63%). However, this higher mortality rate was thought to be biased by a greater number of patients with disseminated disease in the group treated with combination therapy [55]. In a non-comparative study, combination of LAmB and posaconazole was associated with clinical improvement in 56% of patients with mucormycosis [56]. This was comparable with previously reported clinical response rate with monotherapy (32–59%) in the literature [5, 6, 26]. More recently, a study of 10 patients with mucormycosis reported a survival benefit with the combination of LAmB plus posaconazole compared with LAmB monotherapy, although the sample size was small [57•]. Of those who received combination therapy, four of six survived, with none surviving in those who received monotherapy (none of four).

The combination of isavuconazole with an echinocandin has been studied in the animal model without demonstrable synergy [58]. Triple combination with LAmB, posaconazole, and caspofungin was successfully used with surgery to treat a patient with disseminated *Lichtheimia* infection [59]. Recently, a pediatric patient with disseminated *Cunninghamella* was also successfully treated with surgery and combination of LAmB, isavuconazole, and caspofungin [60].

Finally, a large study of 106 hematologic patients receiving various monotherapy and combination therapy conducted a propensity score analysis and did not observe a survival benefit with any combination therapy over monotherapy [61]. However, those receiving combination therapy with amphotericin B and posaconazole had a higher survival rate compared with those receiving monotherapy (24/32 survived vs. 27/47, respectively). In this study, the most common combination was LAmB with echinocandin (46%), followed by LAmB with posaconazole (27%) and triple combination with LAmB, posaconazole, and echinocandin (27%). However, because of the heterogeneity of the study subgroups, it is difficult to draw firm conclusion from these results. As such, combination therapy with LAmB with posaconazole may be more efficacious than AmB monotherapy, although further investigation is warranted.

Taken together, the clinical benefit of combination therapy remains uncertain. However, in the face of a rapidly fatal disease, the potential benefit seems to outweigh the costs and potential toxicity. Currently, the Sixth European Conference on Infections in Leukemia (ECIL-6) and the American Society of Transplantation-Infectious Disease Community of Practice (AST-ID COP) guidelines recommend consideration of combination therapy using LAmB with caspofungin or posaconazole in patients who do not respond to first-line treatment [24, 62].

Novel antifungal agents

VT-1161 is a novel azole agent (tetrazole) which acts as small molecule inhibitor of fungal CYP51A. It has been studied for the treatment of onychomycosis, mucocutaneous and vaginal candidiasis, and coccidioidomycosis [63–65]. This agent also has in vitro activity against Mucorales [66, 67]. Other novel antifungal agents that have in vitro activity against Mucorales include AR-12 (a celecoxib derivative) [68] and APX001A (formerly E1210), an inhibitor of Gwt1p, an important protein in fungal cell wall integrity [69]. These agents

are still in development and are not yet available for clinical use.

Surgical debridement

Of major importance, extensive early surgical debridement is generally recommended in combination with antifungals [24, 25]. Rhino-orbito-cerebral mucormycosis nearly always require surgical debridement to improve outcome [70, 71]. Extensive and repeated interventions may be required to debride all necrotic tissue for adequate disease control. Ocular mucormycosis may be treated by exenteration; however, it does not improve survival [72]. Pulmonary mucormycosis may be managed with medical therapy alone unless necrosis is extensive or in case of life-threatening hemoptysis [73]. Post-traumatic wound infection should be managed with surgical debridement as infection spreads rapidly leading to extensive necrosis with poor penetration of antifungal agents [74].

Reversal of immunosuppression

Glycemic control is mandatory in diabetic patients with rhinocerebral mucormycosis. In diabetic ketoacidotic patients, sodium bicarbonate may be considered as animal studies suggest that it has both iron-chelating and neutrophil function improvement effect [75]. In SOT patients, steroids and other immunosuppressive agents should be lowered to improve patient immunity.

Adjunctive therapy

Iron overload is a risk factor for mucormycosis [76]. Animal studies suggested that deferasirox, an iron-chelating agent, was an effective treatment against mucormycosis of diabetic ketoacidotic mice [77]. Small clinical studies suggested similar effect in patients with mucormycosis [78–80]. However, a randomized, double-blinded, placebo-controlled trial (DEFEAT study) compared deferasirox versus placebo combined with LAmB for the treatment of mucormycosis in 20 patients and reported higher mortality rate with deferasirox (82% vs. 22%, $P = 0.01$) [30]. The small sample size and the imbalance of baseline characteristics (more neutropenic and pulmonary disease in the deferasirox group) between groups were notable limitations. As such, current European guidelines recommend against using deferasirox as adjunctive therapy [24, 25]. Clioquinol, a zinc chelator, also demonstrated in vitro synergistic effect with antifungal agent against *Rhizopus microspores* [81]. However, this effect was found only in combination with posaconazole (but not with AmBd) and was only described with *Rhizopus* sp. (not with other species). To date, there are no clinical data to support the use of this agent. Hyperbaric oxygen therapy has been used successfully in a small number of patients with rhinocerebral mucormycosis [82, 83]. However, quality of evidence is too low to draw firm conclusion regarding the efficacy of this modality. Granulocyte macrophage colony-stimulating factors (GM-CSFs) have also been used in a small number of patients with clinical success [84]. Finally, a recent case report described a patient with extensive abdominal mucormycosis refractory to surgery and combination antifungal therapy who was successfully treated with interferon-gamma and nivolumab, a human IgG4 anti-PD1 monoclonal antibody [85]. The authors hypothesized that these agents help restore patient's monocyte and T cell function, respectively.

In conclusion, current guidelines recommend LAmB at 5 mg/kg/day as first-line therapy for invasive mucormycosis [24, 62]. Higher dose may be considered for central nervous system disease. Isavuconazole or posaconazole are acceptable alternatives for patients who are intolerant to LAmB or who need prolonged oral maintenance therapy. Combination therapy may be used in severe or refractory cases. Extensive surgical debridement is crucial, and immunosuppressive agents should be tapered to lower dose.

Invasive fusariosis

Fusarium is the second most common non-*Aspergilllus* mold infection in the USA, Europe, and Asia [1, 86–88]. In Australia and Newzealand, it has been reported as the third common non-*Aspergillus* mold infection after *Mucorales* and *Scedosporium* [4]. In contrast, it is the most prevalent invasive mold infection in Brazil [89]. There are more than 50 *Fusarium* species, but only few cause human disease [90, 91]. Most species causing diseases in human belong to one of the following complex: *Fusarium solani* complex, *Fusarium oxysporum* complex, and *Fusarium fujikuroi* complex (which comprise *F. verticilloides* [formely *F. moniliformis*] and *F. proliferatum*) [92]. *F. solani* complex is the most common, found in up to 50% of cases of invasive fusariosis, followed by *F. oxysporum* complex which is found in 20% of cases. Direct inoculation and airborne uptake of environmental spores (found in air, tap water, sinks, and showerhead) are the most common routes of infection [90]. *Fusarium* can cause diseases in both immunocompetent and immunocompromised individuals. Clinical presentation in immunocompetent hosts includes keratitis and onychomycosis [93, 94]. In immunocompromised hosts, fusariosis usually presents with pulmonary, sinus, or disseminated disease [90]. Fungemia is observed in 60% of disseminated disease, and necrotic skin involvement is observed in 50–80% of cases [95, 96]. Neutropenia is the most important risk factor for disseminated disease [97]. Historically, fusariosis was associated with a high fatality rate of 79–87% [97, 98]. However, improved outcomes have been reported in the last decade [99].

On histopathology, *Fusarium* is indistinguishable from *Aspergillus*, with the presence of hyaline septate hyphae with acute-angle branching. Galactomannan and the beta-D-glucan assay may be positive but is not specific for *Fusarium* [100–102]. Diagnosis is based on culture, and *Fusarium* is easily identified by the presence of banana-shaped macroconidia. Species identification is done by DNA sequencing or by MALDI-TOF analysis [103]. *Fusarium* species have higher MICs to all antifungal agents compared with *Aspergillus*, and resistance patterns differ significantly among species [104, 105]. Therefore, accurate speciation, as well as antifungal susceptibility testing, should be performed on clinical isolates to guide therapy, even in the absence of CLSI or EUCAST susceptibility breakpoint [106–108]. In vitro data indicate that AmB, voriconazole, posaconazole, and isavuconazole are the most active agents against *Fusarium* [109]. Importantly, there are significant MIC differences between *F. solani* and *F. oxysporum*, suggesting antifungal susceptibility difference between subspecies, adding to the complexity of treatment. For instance, *F solani* complex typically exhibits pan-azole resistance but has somewhat lower MIC against polyene compared with other species. Other species display variable antifungal

susceptibility patterns [110]. As such, antifungal susceptibility testing is of utmost importance to guide choice of antifungal therapy.

Treatment of *Fusarium* infection is challenging due to its inherent resistance to most antifungals and the rarity of clinical trial data on treatment efficacy. In the past two decades, therapeutic options against *Fusarium* spp. have evolved considerably. Early appropriate treatment is crucial which includes early systemic antifungal therapy, surgery, and reversal of immunosuppression.

Early antifungal therapy

The optimal therapy for fusariosis remains uncertain due to the lack of data from clinical trials [111]. Because of the variable susceptibility to antifungals, empirical therapy against fusariosis should include a combination of antifungals such as LAmB and voriconazole, while waiting for antifungal susceptibility testing.

Polyenes

Historically, AmBd was the primary agent used to treat invasive fusariosis. However, the response rate associated with polyene therapy (AmBd, ABLC, or LAmB) was low, varying between 32% and 46% [97, 98, 112]. In a cohort of 84 patients, 90-day mortality rate was 79% and the majority (89%) of deaths were due to fusariosis. In the largest retrospective cohort study of 233 cases of fusariosis reported between years 1985 and 2011, 90-day survival rates with AmBd, LAmB, and voriconazole were 28, 53, and 60%, respectively [99]. Of note, AmBd was commonly used in the early period during which mortality rate tended to be higher (1985–2001); however, the study was not designed to assess the specific efficacy of individual antifungal agent.

Triazoles

Voriconazole has good in vitro activity against *Fusarium* spp., with the exception of *F. solani* complex and *F. verticilloides* [90]. Following its approval in 2002, voriconazole has been used increasingly for the treatment of fusariosis. Perfect et al. assessed the use voriconazole salvage therapy in 11 patients with refractory fusariosis and reported a global response rate of 45% [113]. The largest study on the use of voriconazole for treatment of fusariosis included 73 patients among which 22% were treated with voriconazole as primary therapy. The overall success rate was 47%, further supporting that voriconazole is an acceptable therapeutic option for invasive fusariosis [114].

Posaconazole is another triazole with potent activity against *Fusarium* spp. [115]. While there is no data supporting the use of posaconazole as primary therapy for fusariosis, there are reports on its use as salvage therapy [116–118]. A retrospective analysis of 21 patients from three open-label clinical trials assessed the efficacy of posaconazole as salvage therapy (for refractory disease or intolerance to AmB) and reported successful outcome in 48% of patients [119].

Isavuconazole, a novel triazole, has variable in vitro activity against *Fusarium* spp. Although low isavuconazole MICs were seen in some *Fusarium* isolates, the MIC_{50} values were equivalent to or higher than corresponding values of voriconazole and posaconazole [31, 120]. Nevertheless, isavuconazole has been successfully used in patients with fusariosis with 50% survival rate among

four cases with *Fusarium* and survival in a patient with *Aspergillus* co-infections [121, 122]. Further studies are warranted to demonstrate the efficacy of isavuconazole against fusariosis.

Combination therapy

The data on combination therapy for fusariosis is very limited and mostly based on anecdotal experience. In vitro data suggest most favorable synergy with combination of voriconazole and terbinafine (79% of tested strains), followed by the combination of polyene and voriconazole (17% of tested strain) [123].

In clinical practice, the most commonly used combination is that of polyene with voriconazole, despite the theoretical concern for potential antagonism between polyene with voriconazole (due to the voriconazole-induced inhibition of ergosterol synthesis which is the main target of AmB) [124]. In total, eight case reports have used the combination of polyene with voriconazole and all reported clinical response [125–131]. In a recent case series of five patients with fusariosis, two patients treated with LAmB died while three patients treated with voriconazole monotherapy or in combination therapy (with LAmB or terbinafine) survived at day 180 [57•]. Interestingly, treatment with voriconazole, whether alone or combined, was associated with a trend for improved survival, although this was based on a very small number of patients (three of three survived, while both patients who did not receive voriconazole did not survive; $P = 0.100$).

Clinical use of terbinafine for treatment of invasive fusariosis is limited [132, 133]. In a recent cohort of 15 patients with fusariosis treated with various antifungal combinations, four patients received a combination of voriconazole and terbinafine: two had partial response while two failed therapy [134]. In this same study, two patients were unsuccessfully treated with triple combination therapy with LAmB, voriconazole, and terbinafine. As such, while in vitro data suggest potent activity of terbinafine in combination with other antifungal agents, clinical studies have reported modest result.

Fusarium are intrinsically resistant to echinocandins [106]. Interestingly, in vitro data suggest synergy between LAmB and caspofungin [135, 136]. One surprising report described a patient with acute myeloid leukemia with refractory *Fusarium* fungemia despite AmBd which was successfully eradicated with caspofungin [137]. This report was the initial evidence suggesting the potential utility of caspofungin for treatment of *Fusarium* spp. Subsequently, combination of LAmB and caspofungin has been used to treat refractory fusariosis in two case reports: one patient had complete response while the other patient had initially partial response but subsequently died [138, 139•] Recently, triple combination therapy has been suggested for treatment of *Fusarium solani* based on in vitro data where triple combination therapy (LAmB, voriconazole, and caspofungin) resulted in greater synergy than bitherapy (LAmB + voriconazole) [136].

As such, several antifungal combinations have been used successfully for the treatment of fusariosis. However, the benefit of combination therapy has not been consistently shown and requires further investigation.

Novel antifungal agents

Novel antifungal agents active against *Fusarium* are in development and include E120, F901318, and hemofungin [140]. Interestingly, polymyxin B, an

Table 1. Treatment options of invasive mucormycosis and fusariosis

	Mucormycosis	Fusariosis
First-line agent	- L-AMB or ABLC 5 mg/kg/day IV - Isavuconazole 200 mg oral/IV every 8 h for six doses then 200 mg oral/IV once daily	- Voriconazole 6 mg/kg oral/IV for two doses then 4 mg/kg oral/IV every 12 h - L-AMB or ABLC 5 mg/kg/day IV
Salvage therapy	- Posaconazole 300 mg/day oral/IV	- Posaconazole 300 mg/day oral/IV - Voriconazole 6 mg/kg oral/IV for two doses then 4 mg/kg oral/IV every 12 h
	- LAmB + caspofungin (*most recommended combination*) - LAmB + posaconazole	- LAmB + voriconazole (most recommended combination) - LAmB + terbinafine - LAmB + caspofungin
Surgery	- Consider especially in rhinocerebral mucormycosis	- Consider if feasible
Reversal of immunosuppression	- Correct neutropenia - Taper immunosuppressive agents	- Correct neutropenia - Taper immunosuppressive agents
Adjunctive therapy	- G-CSF/GM-CSF - Hyperbaric oxygen - Sodium bicarbonate	- G-CSF/GM-CSF - Granulocyte transfusion

antibacterial agent, also has fungicidal activity against *Fusarium* [141].

Prophylaxis after targeted therapy

Patients who recover from invasive fusariosis may relapse if exposed to subsequent immunosuppressive therapy. In a retrospective study of 40 patients who survived an initial episode of fusariosis and were subsequently exposed to immunosuppressive therapy, 12.5% experience relapse and all those who relapsed developed fatal disseminated disease. Among the 40 patients, 32 received secondary prophylaxis and voriconazole was the most commonly used agent. In the absence of prophylaxis, 100% of those with disseminated fusariosis experienced relapse compared with 11.5% of those who received secondary prophylaxis ($P = 0.03$) [142]. As such, patients who survived invasive fusariosis and need to be treated with immunosuppressive therapy should receive secondary prophylaxis.

Surgical debridement

Surgery should be considered if feasible. Few case reports showed that surgical resection improved outcome of patients with pulmonary fusariosis [143, 144]. Catheter should be removed in case of catheter-associated infections [145].

Reversal of immunosuppression and adjunctive therapy

Reversal of immunosuppression is crucial in the management of invasive fusariosis. Persistent neutropenia and use of corticosteroids are associated with a fivefold and twofold increased mortality, respectively [98]. Granulocyte colony-stimulating factor (G-CSF) may be considered in patients with

prolonged neutropenia, and immunosuppressive agents should be tapered as much as possible [90, 146]. Granulocyte transfusion has been used successfully [147].

As such, invasive fusariosis should be treated with either voriconazole or LAmB. European guidelines suggest using voriconazole or LAmB as first-line therapy in hematologic patients with invasive fusariosis [105]. The AST-IDCOP guidelines recommend voriconazole as first-line therapy in solid organ transplant recipients with fusariosis due to a better strength of evidence and lower side effects [62]. Posaconazole may be considered in salvage settings. Combination therapy may also be used in refractory or severe cases. Neutropenia may be corrected by using G-CSF in specific population such as hemotapoietic stem cell transplant recipients, and immunosuppressive agents should be reduced. Secondary prophylaxis should be administered following completion of initial targeted therapy.

Conclusion

Emerging non-*Aspergillus* mold infections including mucormycosis and fusariosis have been increasing due to current use of antifungal prophylaxis with *Candida* and *Aspergillus* coverage. Due to the difficult management of these infections, early diagnosis is important to improve outcome. The mainstay of treatment includes early antifungal therapy, adequate surgical debridement, and reversal of immunosuppression. For a summary of treatment options, see Table 1.

Compliance with ethical standards

Conflict of Interest

P.P. has no conflict of interest.

M.L. received research grant from Pfizer and consultation honoraria from Avir.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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