Mucormycosis treatment: Recommendations, latest advances, and perspectives

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Abstract

Mucormycosis are life-threatening fungal infections especially affecting immunocompromised or diabetic patients. Despite treatment, mortality remains high (from 32 to 70% according to organ involvement). This review provides an update on mucormycosis management. The latest recommendations strongly recommend as first-line therapy the use of liposomal amphotericin B (≥ 5mg/kg) combined with surgery whenever possible. Isavuconazole and intravenous or delayed-release tablet forms of posaconazole have remained second-line. Many molecules are currently in development to fight against invasive fungal diseases but few have demonstrated efficacy against *Mucorales*. Despite *in vitro* efficacy, combinations of treatment have failed to demonstrate superiority versus monotherapy. Adjuvant therapies are particularly complex to evaluate without prospective randomized controlled studies which are complex to perform due to low incidence rate and high mortality of mucormycosis. Perspectives are nonetheless encouraging. New approaches assessing relationships between host, fungi, and antifungal drugs, and new routes of administration such as aerosols could improve mucormycosis treatment.

Keywords

Mucorales, antifungal drugs, nebulization, polyenes, azoles, prophylaxis

Introduction

Mucormycosis are life-threatening invasive fungal diseases (IFD) due to fungi belonging to *Mucorales* order [1]. Mucormycosis lead to many clinical manifestations, ranging from localized to disseminated infection. Pulmonary or disseminated diseases are commonly found in immunosuppressed patients (hematological malignancy, hematopoietic stem cell transplantation), rhino-orbito-cerebral form in diabetic patients, and cutaneous forms in patients having trauma [2]. Other localizations (gastrointestinal, endocarditis, osteoarticular or isolated cerebral infections) are less frequent. Treatment is based on surgery when possible, correction of underlying factors, and aggressive antifungal drug therapy [3]. In contrast to other fungi, few molecules are active. Amphotericin B (AmB), posaconazole (PSZ), and isavuconazole (ISZ) have shown *in vitro* efficacy while voriconazole (VCZ) and echinocandins are inefficient [4,5]. The reference method for antifungal susceptibility testing (AST) is broth microdilution method with the methodology of the European Committee for Antimicrobial Susceptibility Testing (EUCAST) [6] or the Clinical and Laboratory Standards Institute (CLSI) [7]. However, a major concern with AST is the lack of clinical breakpoints. Prognosis remains poor, mortality ranging from 32 to 70%, and is linked to underlying diseases and clinical forms [2]. Therapeutic improvement is therefore mandatory [8]. The aim of this review is to focus on latest recommendations, advances and perspectives on mucormycosis treatment.

Recent and new antifungal drugs

Current recommendations

The European Conference on Infections in Leukemia (ECIL) published mucormycosis treatment guidelines in 2017 [9] and the European Confederation of Medical Mycology (ECMM) provided an update in 2019 [10]. Both societies strongly recommend liposomal Amphotericin B (L-AmB) for first-line treatment in adults (A II) (Table 1). Another lipid formulation, Amphotericin B lipid complex (ABLC) could be used in mucormycosis but without central nervous system (CNS) involvement according to the ECIL (B II) [9]. For neonates and pediatric population, L-AmB and ABLC were strongly recommended as first-line treatment (A II) [10].

One issue to be addressed is the dose regimen of L-AmB. The ECMM recommends 5-10 mg/kg and 10 mg/kg in the event of CNS involvement [10]. In a prospective pilot study (Ambizygo), high doses of L-AmB were tested as first-line treatment of mucormycosis [11]. Response rate was 43% (12/28) in patients who received ≥ 7.5 mg/kg/day during the first week compared with 0% (0/5) in patients who did not. A high dose of L-AmB (10mg/kg), combined with surgery in 71% of cases, led to an overall response rate of 36% at week 4 and 45% at week 12. Compared to another study using L-AmB ≥ 5 mg/kg in mucormycosis treatment, response was similar at week 4 (36% vs 40%) but was better at week 12 (45% vs 35%) [12]. Mortality rates were equivalent at week 12 (38% vs 42%). A major side effect with L-AmB high dose was creatinine level doubling in 40% of patients.

The ECMM recommended dose should not be slowly increased over several days but a full dose must be given from the first day of daily treatment [10].

ISZ per os (PO) or intravenous (IV), PSZ delayed-release (DR) tablets or IV forms have been recommended with moderate strength (B II) and PSZ oral suspension have been marginally

recommended (C II) [10]. Moreover, the ECMM strongly discouraged the use of AmB deoxycholate (AmBd) (D II).

Treatment should be started as soon as possible, as delayed AmB therapy is linked to increased mortality [13]. Moreover, it must be continued until complete response on imaging and permanent reversal of immunosuppression [10]. Treatment duration necessary to treat mucormycosis is unknown and further studies are needed to better determine it. To facilitate treatment in stable disease, ISZ PO or PSZ DR tablets are strongly recommended. Time between induction phase with AmB and introduction of azoles depends on clinical and imaging responses. Some authors recommend at least 3 weeks of induction with parenteral AmB [14].

The ECMM has addressed recommendations concerning prophylaxis (Table 2). In neutropenic or GvHD, PSZ DR tablets or IV form are moderately supported (B II, B III) and PSZ oral suspension marginally recommended (C II) while ISZ is marginally supported in neutropenic patients (C II). Finally, in solid organ transplant (SOT) recipients, PSZ and ISZ are marginally recommended in prophylaxis (C III, C II).

Recent drugs

ISZ, a new azole, was approved in the United States and in Europe in 2015 for the treatment of mucormycosis [3,15]. ISZ is available in oral and IV formulations, and presents some advantages: linear pharmacokinetics, few interactions with cytochrome P450 isoenzymes leading to few drug–drug interactions, QT decrease, no nephrotoxic cyclodextrin in the IV formulation (different from posaconazole IV form), no need for dose adjustment in kidney or liver failure and in obesity, and excellent oral bioavailability with no food requirements [3]. Although ISZ has shown higher minimal inhibitory concentrations (MIC) than posaconazole [16], it is demonstrably as effective as AmB to decrease fungal burden and to improve survival in a neutropenic mouse model of mucormycosis [17]. ISZ was tested in VITAL study, a phase 3, single-arm, open-label, non-comparative study. This study assessed safety and efficacy of ISZ in the treatment of mucormycosis [18]. Case-control analysis with historic controls treated with AmB included in the Fungiscope registry showed similar survival benefit. However, some biases are noticeable. A total of 21 patients treated with ISZ were compared to 33 matched controls who had received AmB. AmB was administered through AmBd formulation in 7 controls. This formulation is appreciably less efficient than the liposomal one. Other drawbacks could be emphasized in the use of ISZ. Breakthrough *Mucorales* infections in patients receiving ISZ have been reported [19]. Moreover, some authors have shown in *Drosophila* model of mucormycosis that preexposure to ISZ enhances the virulence of *Mucorales* [20,21]. In a large study including 147 patients, ISZ prophylaxis was less effective than VCZ or PSZ against IFD. Two patients who received ISZ as prophylaxis presented mucormycosis [22]. Although ISZ seems to be less hepatotoxic than other mould-active azoles and present a better tolerance profile than L-AmB [23], the ECMM recommends only moderately ISZ as first-line treatment [10].

Regarding central nervous system (CNS) infections, treatment is based on L-AmB due to clinical experience and *in vitro* data [24]. It has been demonstrated that ISZ penetrates the blood-brain barrier in animal models [25], while AmB displays limited penetration. Concentration of ISZ in the necrotic center of brain abscess has been shown low, but concentration in inflammatory brain tissue surrounding the abscess was adequate, equivalent to predicted plasma concentration [26]. A

recent retrospective study has shown that ISZ is effective in *Mucorales* CNS infections [27]. This result has to be confirmed with larger studies.

IV and DR tablets of PSZ were recently developed and lead to better bioavailability and drug exposure than previous oral solution [28–30]. This increased drug exposure has been related to increased PSZ efficiency [31]. Moreover, DR tablets lead to less variability in absorption and compared to oral suspension are not affected by food [32]. Due to higher serum level, suspension DR tablets and IV forms are moderately recommended while oral suspension is only marginally recommended by the ECMM as first-line treatment [10]. There is no safety concern compared to oral suspension for the two new forms, since there is no correlation between serum level and safety [29–32]. However, IV form is solubilized in cyclodextrin and may lead to renal issues [31]. In a matched-paired analysis of patients treated for invasive mucormycosis, new formulations of PSZ were evaluated [33]. The authors showed that PSZ new formulations are as effective as AmB as first-line treatment and as oral suspension in salvage therapy. However, these results should be interpreted with caution. Numerous biases can be noted such as small sample size, retrospective design, heterogeneity of infectious sites, lack of drug monitoring, and pre-exposure to other antifungal drugs.

Routine therapeutic drug monitoring (TDM) is strongly recommended for patients treated by PSZ [10]. Serum trough PSZ concentrations of 1 mg/L or higher are recommended. However, there is currently no conclusive evidence for routine TDM with ISZ. It could be useful in case of suspected toxicity, treatment failure, drug interactions, obesity, or after a switch from IV to PO therapy [10].

New drugs

Some new antifungal drugs are under clinical evaluation include Rezafungin, SCY-078, orolofim, and encochleated amphotericin B [34]. Rezafungin, a new echinocandin has not been tested against *Mucorales*. SCY-078, member of a new glucan synthase inhibitor subclass is poorly or not active against *Mucorales* [35]. Olorofim is a member of the orotomides, a new antifungal class inhibiting dihydroorotate dehydrogenase (DHODH), a key enzyme in pyrimidine biosynthesis. It is also poorly active against *Mucorales* [36]. Encochleated amphotericin B is a new oral formulation of amphotericin B [34]. It has been shown to be well-tolerated, and is currently tested for cryptococcosis treatment in developing countries (clinical trial NCT04031833). No studies on *Mucorales* efficacy are available.

Other antifungal drugs with activity against *Mucorales* are being developed. VT-1161 is a novel inhibitor of the fungal CYP 51 with *in vitro* activity against *Mucorales*. VT-1161 used as curative or prophylactic treatment has prolonged survival of neutropenic mice in *R. arrhizus* models [37,38]. SCH 42427 a broad-spectrum triazole was found to be effective in a murine model [39]. APX001A (Fosmanogepix) (formerly E1210) is an antifungal agent targeting protein Gwt1. Gwt1 is a surface protein of the glycosylphosphotidyl inositol post-translational modification pathway. Although MICs against *Mucorales* are high [40,41], several authors have shown that APX001A is as effective as AmB to protect mice in a *R. delamar* model [3,42]. Finally, PC1244 a new long-acting fungicidal azole, has shown antifungal activity against *Mucorales* with MICs from 0.25 to 2 mg/L [43] but has not been tested *in vivo*. Among antibiotics, colistin has presented modest *in vitro* and *in vivo* activity against *Mucorales* [44].

New therapeutic approaches

New approaches have recently emerged regarding relationship between fungus, antifungal agent, and host [45]. For example, some authors have emphasized the capacity of PSZ to accumulate within leukocyte membrane due to its lipophilic properties. Cells from HL-60 leukemia cell line differentiated to neutrophil-like phenotype have been loaded with PSZ and used in an aspergillosis mouse model to deliver PSZ directly to the infectious site [46]. However, this new approach has not been tested in a *Mucorales* model. Bioengineering has made great improvement, especially in genetically modified cytotoxic T-cells. These modified cells can specifically target beta-glucan of fungus cell wall [47]. However, this approach has only been tested in an aspergillosis model.

Recently, a *Mucorales* peptide named CotH3 was found to be linked to mucormycosis endothelial invasion by binding the endothelial cell receptor GRP78. Authors generated antibodies against CotH3 to prevent endothelial invasion. Anti-CotH3 antibodies protected neutropenic and diabetic mice from mucormycosis and acted synergistically with antifungal drugs [48]. Moreover, other authors have shown that blocking GRP78 cell receptor by GRP78-specific immune serum may protects diabetic mice from mucormycosis [49]. This peptide-receptor interaction may be a new therapeutic way of research.

New concepts may guide antifungal prophylaxis.

Several authors have hypothesized that *Mucorales,* such as *Histoplasma sp* or *Cryptococcus sp,* can remain latent in immunocompetent patients and lead to active disease when a patient becomes immunosuppressed [50,51]. Authors have shown that *Mucorales* spores might remain dormant in cutaneous granulomatous lesions in an immunocompetent rabbit model [52] and inside innate granuloma in a Zebrafish model [51]. In the event of immunodepression, spores were reactivated. In a murine model of latent mucormycosis, L-AmB was effective to prevent reactivation in *Lichtheimia corymbifera* colonized mice [53]. This concept must be verified in human to evaluate if decolonization of patients before immunosuppression could reduce the risk of reactivation.

Combinations

Combination are not currently recommended for first-line therapy due to lack of evidence of their efficacy (C II, C III) (Table 1) [54]. They could nonetheless represent a major way of increasing antifungal treatment efficacy [55].

Combinations of antifungal agents have been largely tested *in vitro*. Most combinations were indifferent, except for AmB + caspofungin (CAS), PSZ + CAS and ISZ + CAS which were synergistic [55–57]. For azoles + echinocandins, few *in vivo* studies have been performed, showing lack of synergy [58,59]. Among AmB + echinocandins, more data are available *in vivo*. *In vitro* data have been confirmed in a ketoacidotic mouse model where L-AmB and echinocandins (micafungin and anidulafungin) appeared synergistic [60]. Combination of L-AmB and echinocandins prolonged survival and decreased fungal burden of mice in an IV model of *Rhizopus arrhizus* infection. These data were confirmed with ABLC + caspofungin in a ketoacidotic mouse model with improvement of

survival but without fungal clearance in organs [61]. Case reports of combinations have been published and five retrospective clinical studies have been performed on antifungal combinations. AmB + CAS and/or PSZ combinations have been evaluated. Four of the five studies showed indifference [62–65] and one showed synergy [66]. However, the latter included only rhino-orbito-cerebral forms and a small number of patients.

Some non-antifungal agents combined with antifungals drugs have shown interesting synergy. Iron chelators have shown high synergy with antifungal drugs *in vitro* and *in vivo* [59,67,68], but this has not been confirmed in patients [12]. Calcineurin inhibitors (cyclosporine A and tacrolimus), which have immunosuppressive effects, have shown synergy with AmB, PSZ or ISZ *in vitro* and *in vivo* [69–71]. Other agents such as MGCD290 (a Hos2 Histone Deacetylase Inhibitor), not yet FDA-approved, have shown synergy *in vitro* with PSZ [72]. Although lovastatin has shown synergy *in vitro* and *in vivo* with voriconazole [73], the latter is known to enhance *Mucorales* virulence [21]. Ciprofloxacin and fluconazole have shown synergy in mouse models [74], while miltefosine and azoles, and rifampicine and AmB have presented synergistic effects *in vitro* on ≤ 50% [75] and 56 to 83 % [76,77] of tested strains respectively.

Randomized, placebo-controlled clinical trials are needed to determine combination therapy efficacy [78]. Added toxicity, drug interactions, and cost-benefit balance of combinations remain unclear [10].

Adjunctive treatment

Current recommendations

The ECMM and the ECIL-6 strongly recommend surgery and control of underlying disease including management of ketoacidosis and hyperglycemia in diabetic patients, modulation of corticosteroids and immunosuppressive drugs, and reduction of neutropenia duration using hematopoietic growth factor if possible (A II, AII) (Table 3) [9,10]. Granulocyte colony-stimulating factor (G CSF) and hyperbaric oxygen are moderately recommended in case of neutropenia and in diabetic patients respectively (B II), while iron chelators are strongly discouraged.

Surgery

Surgery remains easier to perform in rhino-orbital or cutaneous localizations than in cerebral, pulmonary or disseminated disease. Surgery is precluded in critical ill patients [79]. In patients with unifocal pulmonary mucormycosis, lobectomy or pneumonectomy have provided benefit [80]. However, in case of multifocal or close to great vessels lesions, benefit is less established and surgery is most complicated to perform. In rhino-orbito-cerebral forms, surgery is strongly linked to treatment outcome [81,82]. In a clinico-epidemiological review over 10 years, surgery was performed in 65.2 % of 184 patients but only in 21.4 % of hematological patients [83]. Surgical debridement in combination with medical therapy was associated with a better outcome than medical therapy only. Attention must be paid to the fact that only retrospective studies and epidemiological data are available. However, the benefits of surgery are presumed and is highly recommended whenever possible (A II) [10].

Adjunctive therapies

Adjunctive therapy is used to reverse immunosuppression. Granulocyte (macrophage) colony-stimulating factor (G(M)-CSF) or interferon-γ increases the activity of granulocytes against *Mucorales* such as hyphae damage [84,85]. However, several authors have shown that G-CSF or GM-CSF did not improve antifungal activity of PSZ or L-AmB in a neutropenic murine model [86,87]. Clinical data on this topic are very poor and few cases are published [88–91]. Clear benefit has yet to be established.

Iron chelators have been tested in adjunctive therapy as means of reducing iron availability and thereby inhibiting fungal growth. Deferoxamine, an iron chelator, has been associated with increased mucormycosis incidence. Deferoxamine acts as a xenosiderophore, whereas the two other iron chelators, deferiprone and deferasirox, do not [92]. Ibrahim *et al.* have shown that deferiprone protected diabetic mice from mucormycosis [93]. Deferasirox shared the same effect in diabetic and neutropenic mice and acted synergistically with AmB [67]. Triple therapy using L-AmB, micafungin, and deferasirox was also found to be effective [94]. Moreover, deferasirox increased PSZ activity in a neutropenic mouse model [59]. These promising results led to a clinical study assessing deferasirox + LAmB efficacy [12]. However, patients with mucormycosis treated with deferasirox + L-AmB had a higher mortality rate at 90 days than patients treated with L-AmB alone. However, patients treated with deferasirox had more active malignancy, neutropenia and corticosteroid therapy compared to the placebo group. Population imbalance between deferasirox and placebo groups did not allow for clear conclusions. Unlike iron chelators, zinc chelators have not shown synergy with AmB and have shown poor synergy with PSZ [95].

Hyperbaric oxygen treatment has been shown to deploy direct antimicrobial activity. It exerts a synergistic effect with antimicrobial agents, and enhances cellular immune system and tissue repair in some infectious diseases [96]. In a mucormycosis mouse model, addition of hyperbaric oxygen to AmB did not improve survival [97]. However, in this model, mice were neither immunosuppressed nor diabetic and infection was performed by IV route. In a review of 28 published cases, authors showed that while hyperbaric oxygen improved survival in diabetic patients, it was ineffective in neutropenic patients [98]. However, hyperbaric oxygen treatment failure may be underestimated due to publication bias. Up until now, there has been no randomized study with control group to evaluate efficacy of hyperbaric oxygen so far.

New routes of administration

Nebulized antifungal agents may be a new way of research to improve mucormycosis therapy. The pulmonary aerosolization of antifungal agents can theoretically increase their concentration at the infectious site, which could improve efficacy while limiting their systemic exposure and toxicity. [99]. Administration of L-AmB aerosol was evaluated in a neutropenic mouse model of *R. arrhizus* pulmonary infection [100]. The authors showed that aerosolized L-AmB is effective as a means of decreasing fungal burden and improving survival when administered from day 1 to 5 after infection compared to placebo. However, aerosolized L-AmB was not compared to systemic L-AmB. More animal studies are needed to assess aerosols efficacy alone and in

combination with systemic treatment. Few human cases of mucormycosis treated with AmB aerosols are reported in the literature [101–105]. AmBd has been the most used formulation. Dosage of nebulized AmBd ranges from 6 mg three times a day to 30 mg twice a week, in combination with AmB systemic treatment and surgical treatment. ABLC has also been used in *Rhizomucor sp* infection treatment (50 mg twice daily) [105].

Topical AmB has been used in a few clinical cases [106–108], particularly in burned patients [109]. It has been employed in different forms: washes [110], 5% sulfamylon–amphotericin B (2 µg/ml) dressings [111], daily topical infusions through dressings (50 mg L-AmB diluted in 1L of sterile water) [112], soaks [113] or gauze soaked in 0.2 % AmB solution [114]. Nystatin cream was used in one case report [115]. AmB nanoemulsion was developped to use AmB as topical route of administration, but it has not been tested on *Mucorales* [116,117]. Other authors have developed nanoemulsions containing surfactant to mechanically disrupt microbial membranes. For example, nanoemulsion NB-201, containing refined soybean oil, water, glycerol, EDTA, Tween 20, and the surfactant benzalkonium chloride has shown *in vitro* activity against *Mucorales* [118].

Other routes of administration for AmB are anecdotal: eye drop in *Mucorales* keratitis [119], oral administration in gastrointestinal mucormycosis [120], intradiaphyseal incorporation cement beads in osteomyelitis [121], intrathecal administration in cerebral abscess [122], percutaneous injection in cutaneous lesions [123].

Conclusion

Mucormycosis treatment recommendations were recently updated by the ECMM. L-AmB remains the first-line drug in mucormycosis therapy. ISZ and new PSZ formulations have been added to the guidelines but remain in second-line treatment following L-AmB due to some remaining issues. Few anti-*Mucorales* drugs are currently under development. Moreover, evidence for adjunctive therapies is scarce and doubts on their effectiveness persist due to a lack of randomized prospective controlled studies. They are particularly complex to implement in a context of low incidence disease. Few advances have been made on mucormycosis treatment. However, empowering new concepts and new routes of administration to fight this devastating disease appear promising and are to be encouraged.

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721 Table 1: Recommendations for treatment of invasive mucormycosis from European Conference on
722 Infections in Leukemia 6 (ECIL-6) (2017) and European Confederation of Medical Mycology (ECMM)
723 (2019), adapted from [9,10].

	ECIL-6 2017	Grade	ECMM 2019	Grade
First-line antifungal therapy				
Liposomal amphotericin B	5mg/kg	B II	5-10 mg/kg	A II
			For CNS involvement: 10 mg/kg	A III
Amphotericin B lipid complex	without CNS involvement	B II	Any without CNS involvement	B II
			SOT: 10 mg/kg	A III
Amphotericin B deoxycholate		C II		D II
Posaconazole		C III	DR tablet or IV: 300 mg b.i.d, day 1; 300 mg/d from day 2	B II
			Oral suspension (4 x 200 mg or 2 x 400 mg)	C II
Isavuconazole			200 mg t.i.d, day 1 -2 ; 200 mg/d from day 3	B II
Combination therapy		C III	Liposomal amphotericin B + caspofungin and/or posaconazole	C II - C III
Control of underlying conditions				
Diabetes	Control of diabetes	A II	Control of hyperglycaemia and Ketoacidosis	A III
Immuno-suppression	Discontinuation/tapering of steroids, reduction of immunosuppressive therapy	A II	Rapidly taper glucocorticosteroid dose to discontinue, if feasible, or reduce dose to minimum required	A II
Surgery				
	Rhino-orbito-cerebral infection	A II	Repeated surgery in addition to antifungal treatment	A II
	Soft tissue infection	A II		
	Localized pulmonary lesion	B III		
	Disseminated infection	C III		

SOT: solid organ transplantation. CNS: central nervous system. DR: delayed-release. IV: intravenous. b.i.d: twice a day. t.i.d: three times a day.

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726 Table 2: Prophylaxis recommendation from European Confederation of Medical Mycology (ECMM)
727 (2019), adapted from [10].

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ECMM 2019			Grade
Primary	Neutropenic, GvHD	Posaconazole DR tablet (300 mg b.i.d day1, 300 mg/d from day2)	B II
		Posaconazole IV (300 mg b.i.d day1, 300 mg/d from day2)	B III
		Posaconazole oral suspension (200 mg t.i.d)	C II
	Neutropenic	Isavuconazole PO or IV (200 mg t.i.d day1-2, 200 mg/d from day3; or 200 mg/d from day1)	C II
	SOT	Isavuconazole PO/IV (200 mg t.i.d day1-2, 200 mg/d from day3; or 200 mg/d from day1)	C II
		Posaconazole IV (300 mg b.i.d day1, 300 mg/d from day2)	C III
		Posaconazole oral suspension (200 mg t.i.d)	C III
	All induction chemotherapy	Liposomal amphotericin B	D I
	Neutropenic or GvHD	Fluconazole, itraconazole, voriconazole	D II
Secondary		Last effective drug in the same patient	A III

SOT: solid organ transplantation. DR: delayed-release. IV: intravenous. PO: per os. GvHD: graft versus host disease. d: day. b.i.d: twice a day. t.i.d: three times a day.

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Table 3: Adjunctive therapy recommendations for treatment of invasive mucormycosis from European Conference on Infections in Leukemia 6 (ECIL-6) (2017) and European Confederation of Medical Mycology (ECMM) (2019), adapted from [9,10].

ECIL-6 2017		**ECMM 2019**	
Adjunctive therapy			
Against use of deferasirox	AII	Deferasirox (other than haematology)	C II
		Deferasirox (haematology)	D II
		Deferoxamine	D II
Hyperbaric oxygen	C III	Exposure to 100% hyperbaric oxygen (haematology)	C II
		Exposure to 100% hyperbaric oxygen (diabetes)	B II
Hematopoietic growth factor if neutropenia	A II	G-CSF (haematology, ongoing neutropenia)	B II
		Granulocyte transfusion (haematology, ongoing neutropenia)	C II
		Granulocyte transfusion + IFNy1b (haematology, ongoing neutropenia)	C III
		GM-CSF (diabetes)	C III
		Adoptive immunotherapy, T cells generated in response to *R. arrhizus* antigens	C III
		Nivolumab + interferon-γ	C III

G-CSF: granulocyte colony stimulating factor. GM-CSF: granulocyte macrophage colony stimulating factor.