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Transplant/Immunocompromised Hosts (M Morales, Section Editor)

Salvage Therapy for the Treatment of Mucormycosis

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Abstract

Purpose of Review We aim to discuss the evidence behind combination therapy as well as to describe the novel antifungals used in the treatment for mucormycosis.
Recent Findings In patients with advanced or refractory invasive mucormycosis, limited data support the use of combination salvage therapy with a polyene backbone plus an echinocandin. Several new antifungal agents have also shown in vitro activity against Mucorales by acting through different mechanisms. VT1161 and VT-1598 are next-generation azoles, termed tetrazoles, that target the fungal cell membrane by inhibiting the CYP51 enzyme with minimal drug-drug interactions. Fosmanogepix (APX001) is a glycosylphosphatidylinositol inhibitor with a broad spectrum of activity. Finally, MGCD290 is a histone deacetylase inhibitor that has shown synergistic effects with azoles and echinocandins.
Summary Mucormycosis is a life-threatening disease. Current guidelines recommend polyenes and certain azoles as first-line treatment along with surgical management and correction of specific host factors. For refractory mucormycosis, there are combination salvage therapy options with evidence from murine models and human case reports; however, there have been no prospective, randomized clinical trials to prove their efficacy. For those intolerant of polyenes and azoles, there are novel drug therapies that have shown in vitro activity against Mucorales, although further investigation is needed to determine if these agents should be used clinically as monotherapy or in combination with existing agents.

Introduction

Mucormycosis is an aggressive, angio-invasive disease caused by fungi of the order Mucorales. The number of species in this Order is large and expanding, but the most common are Rhizopus, Mucor, Lichtheimia (formerly Absidia), Rhizomucor, and Cunninghamella. Five major manifestations of infection occur, including rhino-orbital-cerebral, pulmonary, disseminated, cutaneous, and gastrointestinal. Mucorales are ubiquitous in the environment, and aerosolized spores can enter the human host through inhalation, percutaneous inoculation, or ingestion. Invasive disease primarily affects patients in immunocompromised states such as with hematological malignancies, severe neutropenia, high-dose corticosteroids, uncontrolled diabetes mellitus, solid organ transplants, and deferoxamine therapy [1].

The diagnosis of invasive mucormycosis can be difficult and requires a high degree of clinical suspicion, timely diagnostics, such as radiographic imaging, and histological examination of tissue. Histopathologically, angioinvasion with surrounding tissue infarction is seen along with perineural invasion [2]. In tissue, Mucorales typically appear as broad, ribbon-like hyphae with right-angle branching.

There are evolving strategies for the treatment of mucormycosis. Herein, we highlight a case of invasive mucormycosis successfully treated with dual salvage therapy and discuss the potential role and benefit of combination salvage therapy as well as novel agents in the management of mucormycosis.

Case Review

A 62-year-old man with refractory acute myeloid leukemia (AML) underwent induction and consolidation chemotherapy. His initial course was complicated by disseminated fusariosis secondary to fungal pneumonia with a cavitary nodule that required surgical resection and a prolonged course of posaconazole. After clinical remission, he received a hematopoietic stem cell transplant from a haploidentical, related donor, which was complicated by cytokine release syndrome requiring tocilizumab therapy. He developed chronic graft-versus host disease of the skin, eyes, and oropharynx and was initially treated with tacrolimus and high-dose steroids. Later, ibrutinib was added as a steroid-sparing strategy. He was maintained on posaconazole antifungal prophylaxis during this time.

One month following the initiation of ibrutinib, he was admitted to the hospital with new left eye pain, swelling, and redness and was diagnosed with orbital cellulitis. He reported actively participating in the construction of his own house that involved the demolition of walls. Laboratory workup revealed a white blood cell count of 8.7 K/mcL and creatinine of 1.12 mcg/dL; a serum posaconazole level later returned in the therapeutic range at 2.3 μg/mL. He was initially started on liposomal amphotericin (LAmB) at 3 mg/kg and ampicillin-sulbactam; ibrutinib and steroids were held, and tacrolimus was continued at a reduced dose in order to decrease his overall level of immunosuppression. Magnetic resonance imaging (MRI) demonstrated ill-defined enhancement on the left facial retromaxillary fat, cranial nerve V2, in the medial aspect of the left masticator space, and at the left orbital apex; the posterior aspect of the left ethmoid sinus and left middle and superior turbinates and in the left pterygopalatine fossa and pterygoid bone were also involved; finally, there was enhancement of the left optic nerve sheath with signal abnormality extending into left foramen rotundum.

Although initial endoscopic exam was inconclusive, and histopathologic frozen section was negative for invasive fungal disease, he was ultimately brought to the operating room for re-evaluation and debridement, where poorly perfusing necrotic tissue and positive margins with fungal hyphae were found. Fungal cultures from the operating room were negative, but 18S PCR on paraffin embedded tissue later identified *Rhizopus oryzae*. LAmB was increased to 5 mg/kg and isavuconazole and micafungin 100 mg daily were added for salvage therapy. The patient declined aggressive debridement with left eye enucleation, and antifungal salvage therapy was continued. In addition, hyperbaric oxygen therapy (HBOT) was started, and immunosuppression was weaned. Interval MRI demonstrated progression of disease, and isavuconazole was held due to concerns of antagonism. After a 1-month hospital stay, he was discharged on AmB 5mg/kg daily and micafungin 100 mg daily, as well as HBOT twice weekly.

Two months after discharge, repeat MRI demonstrated further progression of disease. He was briefly started on deferasirox 720 mg twice daily and sargramostim 250 mg subcutaneous daily. His antifungal regimen was continued with LAmB and micafungin. His course was complicated by acute kidney injury requiring adjustment in LAmB dose (5 mg/kg every other day). After approximately 9 months of LAmB and micafungin dual therapy, oral step down to isavuconazole 372 mg daily was made with confirmation of therapeutic drug level of 6.7 mcg/mL. The patient had persistent vision loss in the left eye, and follow-up MRIs demonstrated stable disease. He remains alive and clinically stable 18 months after diagnosis on isavuconazole therapy.

Primary Antifungal Therapy for Mucormycosis

Polyenes and certain azoles along with aggressive surgical debridement have been the established treatment for mucormycosis [3•]. When the lipid formulations, LAmB or amphotericin B lipid complex (ABLC) are not available, standard therapy with amphotericin B deoxycholate (AmB) is the backbone of currently recommended treatment. The optimal dosages for polyenes in the treatment of mucormycosis are not known; however, the recommended starting dose for AmB is 1.0–1.5 mg/kg/day and the recommended starting dose for LAmB and ABLC is 5 mg/kg/day with possible escalation to 10 mg/kg/day in early treatment or if CSF penetration is needed [4•]. A phase I–II study was conducted to determine the maximally tolerated dosage of LAmB in proven or probable fungal infections. Dosage cohorts consisted of 7.5, 10.0, 12.5, and 15 mg/kg of LAmB. A nonlinear relationship was demonstrated between dosage and plasma pharmacokinetic parameters, which reached maximum values with the 10 mg/kg/day dosage and declined at the 12.5 and 15 mg/kg/day dosages [5]. In the AmbiZygo study, 40 patients were enrolled in a prospective pilot study of high-dose LAmB for initial treatment of mucormycosis. Patients received 10 mg/kg/day of LAmB in combination with surgery in 71% of cases, which was associated with an overall response rate of 36% at week 4 and 45% at week 12. Creatinine doubled in 40% of patients but returned to normal within 12 weeks in 63% of these patients [6]. In patients who develop nephrotoxicity secondary to LAmB, changing the dose to every 48 or 72 h is a reasonable strategy [7]. Finally, the pharmacodynamics of 1, 5, and 10 mg/kg/day of ABLC

and LAmB were compared in a neutropenic murine model of invasive pulmonary mucormycosis. At a dose of 10 mg/kg/day, both LAmB and ABLC were effective at reducing fungal lung burden. However, mice treated with ABLC at 5 mg/kg/day had significantly higher AmB lung concentrations than the LAmB-treated mice, which shows higher initial doses of LAmB than ABLC may be required during treatment of invasive pulmonary mucormycosis [8].

After a response to parenteral LAmB for at least 3–4 weeks, patients can be transitioned to an oral azole for consolidation or step-down therapy. Response is generally defined as stability or improvement on repeat imaging, but there are not clear guidelines for this assessment. Of the azoles, posaconazole and isavuconazole have the greatest in vitro activity against most Mucorales [9]. Posaconazole has traditionally been limited by poor bioavailability in earlier formulations, especially for a patient population with erratic absorption due to mucositis, gastrointestinal graft-versus-host disease, poor appetite, nausea/diarrhea, or on acid suppressing agents. However, delayed release tablets have been commercially available since Food and Drug Administration (FDA) approval for fungal prophylaxis in November 2013 [10]. Clinical effectiveness was demonstrated in several small studies. In vitro susceptibility of posaconazole was compared to that of AMB, itraconazole, voriconazole, and fluconazole against 37 clinical isolates of Zygomycetes. The MICs of posaconazole at which 50% and 90% of the isolates were inhibited 0.25 and 4 μg/mL, respectively [11]. Contrary to the in vitro data, published reports of murine models raise concerns about the clinical efficacy of posaconazole. Three isolates of Zygomycetes were used to produce a disseminated infection in immunocompetent mice. Posaconazole had no beneficial effects against *R. oryzae*, partial activity against *Absidia corymbifera*, and dose-dependent efficacy against *Rhizopus microsporus* [12].

Isavuconazole, a newer triazole, has been shown to have good bioavailability, fewer adverse effects, and a proven therapeutic option in the setting of renal impairment. In vitro studies that demonstrate sufficient inhibition of certain isolates of Zygomycetes align with clinical data. In the VITAL study, 37 patients received isavuconazole for a median of 84 days for the treatment of invasive fungal disease. Day-42 crude all-cause mortality in 7 out of the 21 primary-treatment isavuconazole cases was similar to 13 amphotericin B-treated match controls [13••], demonstrating that isavuconazole may be an effective option for the treatment of Mucor disease.

Recommendations:

- AmB, LAmB, and ABLC are primary antifungal agents for mucormycosis. However, LAmB and ABLC are preferred over AmB due to less nephrotoxicity.
- The recommended starting dose for LAmB and ABLC is 5 mg/kg/day.
- Isavuconazole is an orally available triazole commonly used for step-down therapy for mucormycosis.

Combination Salvage Antifungal Therapy for Mucormycosis

In patients who are intolerant to or have invasive mucormycosis that is refractory to monotherapy, combination salvage therapy with a polyene backbone of ABLC or LAmB should be considered [14]. Potential advantages to combination

therapy include broader coverage against Mucorales species and the possibility for a synergistic therapeutic effect. The disadvantages include the possibility of increased toxicity, other drug-drug interactions (especially through cytochrome P450 metabolism with azoles), the possibility of antagonistic interaction between the paired antifungal agents, and increased cost [15].

There are numerous case reports and small case series that have been published suggesting a possible benefit from this combination strategy. For example, in a retrospective cohort study compromised of 10 cases of mucormycosis, 6 patients died but all of the 4 surviving patients had received combination therapy with LAmB and posaconazole (2 of the 6 nonsurvivors also received combination therapy) [16]. Also, Vasquez et al. [17] described a patient with AML and zygomycosis who was initially unresponsive to monotherapy with LAmB but had a favorable outcome with the addition of caspofungin. Similarly, Gargouri et al. [18] reported a case of a 52-year-old woman with invasive mucormycosis treated with surgical debridement and a combination AmB and caspofungin with a good outcome.

There are no prospective, randomized clinical trials to establish efficacy of these strategies. In fact, there is a 20-year retrospective single-institution study where 106 patients with hematological malignancies were diagnosed with mucormycosis. In this study, 44% received monotherapy with either LAmB or posaconazole while 56% received combination treatment with LAmB plus posaconazole or LAmB plus an echinocandin or triple therapy with LAmB, posaconazole, and an echinocandin as initial therapy. The primary outcome was 6-week mortality after treatment initiation. There were no differences in mortality between monotherapy and combination treatment groups, but the combination group with LAmB plus posaconazole did have a higher rate of survival compared to the monotherapy group [19]. This was also evident in a 10-year retrospective study that included 64 patients with either hematological malignancies or hematopoietic cell transplants with proven or probable invasive mucormycosis. Sixty-six percent of patients received surgical debridement. Initial antifungal treatment consisted of lipid formulation of AmB alone (44%), AmB plus posaconazole (25%), AmB plus echinocandin (13%), AmB plus isavuconazole (8%), posaconazole alone (5%), and isavuconazole alone (3%). Although treatment with AmB plus posaconazole or isavuconazole was associated with a trend toward lower treatment failure compared with AmB alone, the all-cause 1-year mortality was not statistically different between AmB versus combination AmB plus posaconazole or isavuconazole [20].

Currently, there are 3 types of combination therapies that have been discussed in the literature and are widely used. Each strategy utilizes the polyene backbone of AmB in combination with one of the following: (1) echinocandin, (2) azole, (3) iron chelator. The evidence for each of these strategies has first been demonstrated in murine models and then applied to human studies.

Echinocandins, which act on the enzyme (1,3)-β-D-glucan synthase (GS) to disrupt the fungal cell wall, generally do not have in vitro activity against Mucorales; however, *R. oryzae* has the genetic homolog of the FSK gene, which encodes for GS. Echinocandins combined with other drugs change the fungal membrane, making this gene more accessible [21]. When combined with ABLC or LAmB, caspofungin therapy was associated with improved outcomes in a small case series of 6 patients with rhino-orbital-cerebral mucormycosis when compared to those who received AmB monotherapy alone [22]. This benefit

was first described in the murine model. A combination of LAmB and micafungin at 1 mg/kg/day synergistically improved survival of diabetic ketoacidosis (DKA) mice with mucormycosis compared to either monotherapy arm. Similarly, combination LAmB and anidulafungin 10 mg/kg/day improved survival in neutropenic mice compared to either monotherapy arm alone [23]. Zhang et al. [24] observed a high rate of synergism when caspofungin was combined with AmB, posaconazole, or itraconazole against *Mucor irregularis* isolates. Additionally, the efficacy of triple therapy using LAmB, micafungin, and deferasirox in a DKA murine model of mucormycosis resulted in significant reductions of brain and kidney tissue fungal burdens compared to monotherapy with each agent or combination therapy with deferasirox and micafungin, deferasirox and LAmB, or LAmB and micafungin [25].

Neither posaconazole nor isavuconazole in combination with a lipid polyene has shown any advantage in salvage therapy for mucormycosis. Posaconazole combined with low dose AmB (0.3 mg/kg/day) prolonged survival and reduced tissue burden in a murine model of *R. oryzae* infected neutropenic mice compared to 0.3 mg/kg/day of AmB monotherapy, however, combination therapy was not superior to AmB given at 0.8 mg/kg/day alone [26]. Likewise, the efficacy of posaconazole plus LAmB therapy was compared to monotherapy with either drug alone in neutropenic or DKA mice infected with *R. oryzae*. There was no evidence of an additive benefit of combination treatment in terms of death or fungal tissue burden in the mice [27].

Combination therapy with isavuconazole and AmB has shown antagonistic activity with certain molds such as Aspergillus and Fusarium and with *Candida glabrata* but indifferent interactions with *R. oryzae* [28, 29]. Moreover, in an in vitro study comparing the activity of isavuconazole plus micafungin combination therapy against placebo, either drug alone, or standard therapy with LAmB when treating pulmonary murine mucormycosis, the combination of isavuconazole with micafungin did not enhance survival over monotherapy but also did not show antagonism [30].

Deferasirox is an oral iron chelator which has in vitro fungicidal properties against Mucorales [31]. While it has proven to be as efficacious as LAmB therapy in DKA mice with disseminated mucormycosis [32], the double-blinded, randomized, placebo-controlled phase II Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study failed to demonstrate a benefit to combination therapy and actually showed an increased mortality in patients treated with adjunctive deferasirox [33••]. Moreover, given its oral formulation, patients with malabsorption issues should not be treated with deferasirox. It has also been associated with renal toxicity. For these reasons, the adjunctive use of deferasirox should probably be avoided.

In Figure 1, we propose a treatment algorithm for the management of invasive mucormycosis.

Recommendations:

- There have been no prospective randomized clinical trials to show differences in mortality between monotherapy and combination therapy.
- ABLC or LAmB combined with an echinocandin has been associated with improved outcomes in case reports of patients with refractory disease caused by mucormycosis.

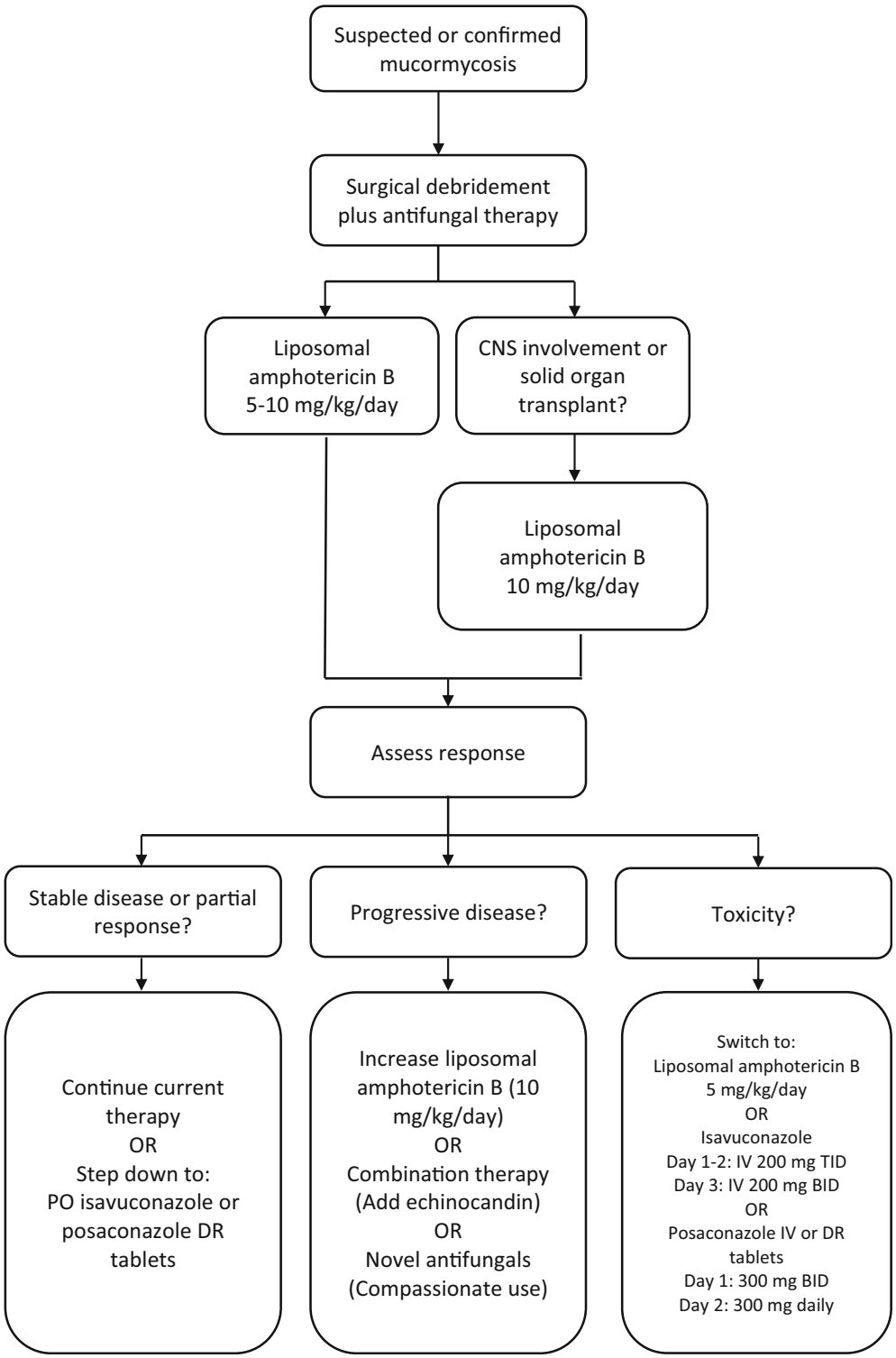

Fig. 1. Proposed treatment algorithm for the management of invasive mucormycosis

- Deferasirox is not recommended in combination therapy given proven increased mortality and renal toxicity.

Novel Antifungal Therapies for Mucormycosis

Another avenue that has been explored in novel therapy for mucormycosis is oteseconazole (VT-1161). VT-1161 is a metalloenzyme inhibitor that targets the biosynthesis of ergosterol by selectively inhibiting fungal Cyp51. In vitro testing has demonstrated that VT-1161 has intrinsic antifungal activity against Mucorales species, particularly *Rhizopus arrhizus var. arrhizus* [34]. VT-1161 in prophylaxis and continuous therapy models has been shown to outperform posaconazole in mice infected with *Rhizopus arrhizus var. arrhizus* [35].

Similarly, VT-1598 is a novel tetrazole-based inhibitor of fungal Cyp51 that disrupts the ergosterol biosynthetic pathway by preventing the conversion of lanosterol to ergosterol. More importantly, VT-1598 is more specific for fungal Cyp51, thus limiting potential drug-drug interactions. In vitro, VT-1598 demonstrated activity against *R. arrhizus* isolates; however, the in vitro potency was reduced in *R. arrhizus var. delemar* strains [36].

Fosmanogepix (APX001), the prodrug of Manogepix (E1210), is another novel antifungal drug that inhibits the fungal enzyme Gwt1, which subsequently inactivates posttranslational modification of glycosylphosphatidylinositol (GPI) anchor proteins. When the GPI-anchor synthesis is disrupted, β-1,3-glucan can be exposed allowing the immune system to recognize the fungus [37•]. APX001 has been shown to be efficacious against both *Rhizopus arrhizus var. arrhizus* and *R. arrhizus var. delemar* strains. In invasive pulmonary infection models, treatment of mice with 78 mg/kg or 104 mg/kg along with 1-aminobenzotriazole to enhance the serum half-life of E1210 increased median survival time and prolonged survival by day 21 post-infection compared to placebo [38].

MGCD290 is a Hos2 fungal histone deacetylase (HDAC) inhibitor that has synergy against molds when combined with various azoles. Despite complete lack of activity of fluconazole against all filamentous fungal isolates when tested alone, synergy was observed with MGCD290 for 40% of Zygomycetes. When tested in combination with voriconazole, MGCD290 showed synergistic activity against 73% of Zygomycetes isolates and when combined with posaconazole, MGCD290 synergistically potentiated its activity against 93% of the isolates [39].

Although none of these novel antifungal agents are currently FDA approved, they are beginning to advance in human clinical trials. VT-1161 is currently in clinical development and undergoing phase 3 ongoing trial. VT-1598 is in its preclinical trial. APX001 is in its phase 2 clinical trial after phase 1 clinical studies demonstrated > 90% bioavailability. Lastly, MGCD290 completed the phase 2 trial and currently has no ongoing trial.

Recommendations:

- VT-1161 and VT-1598 have proven antifungal activity against *R. arrhizus* isolates while limiting potential drug-drug interactions by selectively inhibiting fungal Cyp51.

- APX001 is an intravenously (i.v.) and orally (p.o.) available prodrug that has been shown to have equivalent efficacy to isavuconazole.
- MGCD290, when combined with certain azoles, has demonstrated synergy against molds.

Adjunctive Therapies for Mucormycosis

The latest developments in the treatment of mucormycosis stem from the pathogenesis of this invasive fungal infection. Mucorales invasion is facilitated when certain host factors impair the cytotoxic function of phagocytes [40]. This is evident in patients with functional or quantitative neutropenia. Hence, the adjunctive use of cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) has been reported. Gracia-Diaz et al. [41] describe successfully treating 3 nonneutropenic patients with GM-CSF along with surgical and standard therapy. They recommended the subcutaneous administration of GM-CSF 250 micrograms 3 times a week for nonneutropenic patients.

Furthermore, Mucorales adhere to endothelial cells by expressing the spore coat homolog (CotH) proteins and attaching to the endothelial host receptor GRP78. In acidic, elevated iron, or elevated glucose environments, the expression of this protein and receptor increases. Hence, anti-CotH3 antibodies are also potential adjunctive immunotherapeutic option for advanced disease [42].

Lastly, while this is not a novel therapy, there are reports of successful outcomes with HBOT as adjunctive treatment for serious, invasive mucormycosis, including rhino-cerebral disease. During HBOT, 100% oxygen is administered with pressures at 250–280 kPa resulting in a PaO2 of 1200–2000 mmHg. Patients usually undergo 20–40 sessions with each session lasting 90–120 minutes [43]. In vitro, HBOT inhibits fungal growth at 10 atmospheres absolute while correcting lactic acidosis, which promotes the oxidative action of AmB. Moreover, HBOT promotes tissue healing by increasing tissue oxygen levels and growth factors as well as enhancing leukocyte-mediated phagocytosis [44]. A review of 28 published cases of mucormycosis indicated that HBOT showed an 86% overall survival rate with a 94% survival rate among patients with diabetes but only a 33% survival rate among patients with hematological malignancies and bone marrow transplants [45]. The authors concluded that HBOT may provide some benefit in patients with diabetes but had limited additional efficacy in the patients with hematological malignancies.

Recommendations:

- GM-CSF and anti-CotH3 antibodies are potential immunotherapeutic adjunctive treatment options.
- HBOT adjunctive therapy increases the survival rate from mucormycosis in patients with diabetes, but has limited additional efficacy in hematological malignancies or bone marrow transplant recipients.

Conclusion

Mucormycosis is an aggressive fungal infection that is becoming more common in at-risk, immunosuppressed populations. While definitive guidelines are hard

to produce given the lack of prospective randomized clinical trials, combination therapy with a polyene and echinocandin is likely the most efficacious therapy strategy. There are new antifungals in various stages of development that hold promise for the expansion of effective therapeutics for mucormycosis. Finally, debridement surgery, correction of underlying host factors, and polyene therapy are the current standard of care but as we understand more about these organisms and the hosts they invade, the early detection and treatment of this devastating disease will become more successful.

Declarations

Conflict of Interest
Ashka A. Patel declares that she has no conflict of interest. Jacqueline T. Bork declares that she has no conflict of interest. David J. Riedel declares that he has no conflict of interest.

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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect. 2004;10(Suppl 1):31–47.
2. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. Arch Pathol Lab Med. 2001;125(3):375–8.
3.• Skiada A, Lanternier F, Groll AH, Pagano L, Zimmerli S, Herbrecht R, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica. 2013;98(4):492–50.

Given that mucomycosis is an emerging infectious cause of morbidity and moralabity in patients with hematological malignancies, the European Conference on Infectios in Leukemia developed an evidence-based guideline for the treatment and diagnosis of mucormycosis.

4.• Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis. 2009;48(12):1743–5.

This is a review article that summarizes both the established and novel management strategies of mucormycosis based off of clinical data.

5. Walsh TJ, Goodman JL, Pappas P, Bekersky I, Buell DN, Roden M, et al. Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with Aspergillus species and other filamentous fungi: maximum tolerated dose study. Antimicrob Agents Chemother. 2001;45(12):3487–96.
6. Lanternier F, Poiree S, Elie C, Garcia-Hermoso D, Bakouboula P, Sitbon K, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015;70(11):3116–23.
7. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood. 2011;118(5):1216–24.
8. Lewis RE, Albert ND, Liao G, Hou J, Prince RA, Kontoyiannis DP. Comparative pharmacodynamics of amphotericin B lipid complex and liposomal amphotericin B in a murine model of pulmonary mucormycosis. Antimicrob Agents Chemother. 2010;54(3):1298–304.
9. Arendrup MC, Jensen RH, Meletiadis J. In vitro activity of isavuconazole and comparators against clinical isolates of the Mucorales order. Antimicrob Agents Chemother. 2015;59(12):7735–42.
10. Wiederhold NP. Pharmacokinetics and safety of posaconazole delayed-release tablets for invasive fungal infections. Clin Pharm. 2016;8:1–8.

11. Sun QN, Fothergill AW, McCarthy DI, Rinaldi MG, Graybill JR. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. Antimicrob Agents Chemother. 2002;46(5):1581–2.
12. Dannaoui E, Meis JF, Loebenberg D, Verweij PE. Activity of posaconazole in treatment of experimental disseminated zygomycosis. Antimicrob Agents Chemother. 2003;47(11):3647–50.
13.•• Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR 3rd, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16(7):828–3.

This VITAL study is a single-arm open-label trial that compares the efficiacy and safety of isavuconazole compared to amphotericin B for the treatment of mucormycosis in a matched case-control analysis.

14. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19(12):e405–e21.
15. Sipsas NV, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP. Therapy of mucormycosis. J Fungi (Basel). 2018;4(3).
16. Jenks JD, Reed SL, Seidel D, Koehler P, Cornely OA, Mehta SR, et al. Rare mould infections caused by Mucorales, Lomentospora prolificans and Fusarium, in San Diego, CA: the role of antifungal combination therapy. Int J Antimicrob Agents. 2018;52(5):706–12.
17. Vazquez L, Mateos JJ, Sanz-Rodriguez C, Perez E, Caballero D, San Miguel JF. Successful treatment of rhinocerebral zygomycosis with a combination of caspofungin and liposomal amphotericin B. Haematologica. 2005;90(12 Suppl):ECR39.
18. Gargouri M, Marrakchi C, Feki W, Charfi S, Maaloul I, Lahiani D, et al. Combination of amphotericin B and caspofungin in the treatment of mucormycosis. Med Mycol Case Rep. 2019;26:32–7.
19. Kyvernitakis A, Torres HA, Jiang Y, Chamilos G, Lewis RE, Kontoyiannis DP. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. Clin Microbiol Infect. 2016;22(9):811 e1- e8.
20. Miller MA, Molina KC, Gutman JA, Scherger S, Lum JM, Mossad SB, et al. Mucormycosis in hematopoietic cell transplant recipients and in patients with hematological malignancies in the era of new antifungal agents. Open Forum Infect Dis. 2021;8(2):ofaa646.
21. Ibrahim AS, Bowman JC, Avanessian V, Brown K, Spellberg B, Edwards JE Jr, et al. Caspofungin inhibits Rhizopus oryzae 1,3-beta-D-glucan synthase, lowers burden in brain measured by quantitative PCR, and improves survival at a low but not a high dose during murine disseminated zygomycosis. Antimicrob Agents Chemother. 2005;49(2):721–7.
22. Reed C, Bryant R, Ibrahim AS, Edwards J Jr, Filler SG, Goldberg R, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47(3):364–71.
23. Ibrahim AS, Gebremariam T, Fu Y, Edwards JE Jr, Spellberg B. Combination echinocandin-polyene treatment of murine mucormycosis. Antimicrob Agents Chemother. 2008;52(4):1556–8.
24. Zhang S, Li R, Yu J. Drug combinations against Mucor irregularis in vitro. Antimicrob Agents Chemother. 2013;57(7):3395–7.
25. Ibrahim AS, Gebremariam T, Luo G, Fu Y, French SW, Edwards JE Jr, et al. Combination therapy of murine mucormycosis or aspergillosis with iron chelation, polyenes, and echinocandins. Antimicrob Agents Chemother. 2011;55(4):1768–70.
26. Rodriguez MM, Serena C, Marine M, Pastor FJ, Guarro J. Posaconazole combined with amphotericin B, an effective therapy for a murine disseminated infection caused by Rhizopus oryzae. Antimicrob Agents Chemother. 2008;52(10):3786–8.
27. Ibrahim AS, Gebremariam T, Schwartz JA, Edwards JE Jr, Spellberg B. Posaconazole mono- or combination therapy for treatment of murine zygomycosis. Antimicrob Agents Chemother. 2009;53(2):772–5.
28. Katragkou A, McCarthy M, Meletiadis J, Petraitis V, Moradi PW, Strauss GE, et al. In vitro combination of isavuconazole with micafungin or amphotericin B deoxycholate against medically important molds. Antimicrob Agents Chemother. 2014;58(11):6934–7.
29. Katragkou A, McCarthy M, Meletiadis J, Hussain K, Moradi PW, Strauss GE, et al. In vitro combination therapy with isavuconazole against Candida spp. Med Mycol. 2017;55(8):859–68.
30. Gebremariam T, Wiederhold NP, Alqarihi A, Uppuluri P, Azie N, Edwards JE Jr, et al. Monotherapy or combination therapy of isavuconazole and micafungin for treating murine mucormycosis. J Antimicrob Chemother. 2017;72(2):462–6.
31. Ibrahim AS, Gebermariam T, Fu Y, Lin L, Husseiny MI, French SW, et al. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J Clin Invest. 2007;117(9):2649–57.
32. Lewis RE, Pongas GN, Albert N, Ben-Ami R, Walsh TJ, Kontoyiannis DP. Activity of deferasirox in Mucorales: influences of species and exogenous iron. Antimicrob Agents Chemother. 2011;55(1):411–3.
33.•• Spellberg B, Ibrahim AS, Chin-Hong PV, Kontoyiannis DP, Morris MI, Perfect JR, et al. The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. J Antimicrob Chemother. 2012;67(3):715–2.

DEFEAT Mucor is a randomized trial that concluded that patients with mucormycosis had an increased mortality rate at 90 days when treated with LAmB plus deferasirox compared to LAmB plus placebo.

34. Gebremariam T, Wiederhold NP, Fothergill AW, Garvey EP, Hoekstra WJ, Schotzinger RJ, et al. VT-1161 protects immunosuppressed mice from Rhizopus arrhizus var. arrhizus infection. Antimicrob Agents Chemother. 2015;59(12):7815–7.
35. Gebremariam T, Alkhazraji S, Lin L, Wiederhold NP, Garvey EP, Hoekstra WJ, et al. Prophylactic treatment with VT-1161 protects immunosuppressed mice from Rhizopus arrhizus var. arrhizus infection. Antimicrob Agents Chemother. 2017;61(9).
36. Wiederhold NP, Patterson HP, Tran BH, Yates CM, Schotzinger RJ, Garvey EP. Fungal-specific Cyp51 inhibitor VT-1598 demonstrates in vitro activity against Candida and Cryptococcus species, endemic fungi, including Coccidioides species, Aspergillus species and Rhizopus arrhizus. J Antimicrob Chemother. 2018;73(2):404–8.
37.• Rauseo AM, Coler-Reilly A, Larson L, Spec A. Hope on the horizon: novel fungal treatments in development. Open Forum Infect Dis. 2020;7(2):ofaa01.
This is a review of new therapies against invasive fungal infection currently in clinical development.
38. Gebremariam T, Alkhazraji S, Alqarihi A, Wiederhold NP, Shaw KJ, Patterson TF, et al. Fosmanogepix (APX001) is effective in the treatment of pulmonary murine mucormycosis due to Rhizopus arrhizus. Antimicrob Agents Chemother. 2020;64(6).
39. Pfaller MA, Messer SA, Georgopapadakou N, Martell LA, Besterman JM, Diekema DJ. Activity of MGCD290, a Hos2 histone deacetylase inhibitor, in combination with azole antifungals against opportunistic fungal pathogens. J Clin Microbiol. 2009;47(12):3797–804.
40. Petrikkos G, Tsioutis C. Recent advances in the pathogenesis of mucormycoses. Clin Ther. 2018;40(6):894–902.
41. Garcia-Diaz JB, Palau L, Pankey GA. Resolution of rhinocerebral zygomycosis associated with adjuvant administration of granulocyte-macrophage colony-stimulating factor. Clin Infect Dis. 2001;32(12):e145–50.
42. Gebremariam T, Alkhazraji S, Soliman SSM, Gu Y, Jeon HH, Zhang L, et al. Anti-CotH3 antibodies protect mice from mucormycosis by prevention of invasion and augmenting opsonophagocytosis. Sci Adv. 2019;5(6):eaaw1327.
43. Siddiqui A, Davidson JD, Mustoe TA. Ischemic tissue oxygen capacitance after hyperbaric oxygen therapy: a new physiologic concept. Plast Reconstr Surg. 1997;99(1):148–55.
44. Ferguson BJ, Mitchell TG, Moon R, Camporesi EM, Farmer J. Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis. Rev Infect Dis. 1988;10(3):551–9.
45. John BV, Chamilos G, Kontoyiannis DP. Hyperbaric oxygen as an adjunctive treatment for zygomycosis. Clin Microbiol Infect. 2005;11(7):515–7.

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