

# Recent Advances in the Treatment of Mucormycosis

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**Abstract** In recent years, substantial advances have been achieved in the treatment of mucormycosis. It is now clear that early initiation of therapy results in substantially better outcomes, underscoring the need to maintain a high index of suspicion and aggressively biopsy potential lesions. Increasing data support the need for surgical excision of infected and/or necrosed tissue whenever feasible. Based on their superior safety and efficacy, lipid formulations of amphotericin B have become the standard treatment for mucormycosis. Posaconazole may be useful as salvage therapy, but cannot be recommended as primary therapy for mucormycosis based on available data. Pre-clinical and limited retrospective clinical data suggest that combination therapy with lipid formulations of amphotericin and an echinocandin improves survival during mucormycosis. A definitive trial is needed to confirm these results. The use of the iron chelator, deferasirox, as adjunctive therapy also improved outcomes in animal models of mucormycosis. However, its efficacy was not confirmed in a recent, phase 2 clinical trial. Additional study is required of the potential for abrogation of iron acquisition as adjunctive treatment of

mucormycosis. Combination polyene-posaconazole therapy was of no benefit in pre-clinical studies. Adjunctive therapy with recombinant cytokines, hyperbaric oxygen, and/or granulocyte transfusions can be considered in selected patients. Large-scale, prospective, randomized clinical trials are needed to define optimal management strategies for mucormycosis.

**Keywords** Mucormycosis · Amphotericin · Liposomal amphotericin · Amphotericin B lipid complex · Posaconazole · Echinocandins · Deferasirox

## Introduction

Mucormycosis is a life-threatening infection caused by fungi of the order Mucorales. Recent re-classification has abolished the class Zygomycetes and placed the order Mucorales in the subphylum Mucormycotina [1]. Therefore, we refer to infection caused by Mucorales as mucormycosis rather than zygomycosis.

Mucormycosis typically occurs in patients with diabetes mellitus, organ or hematopoietic stem cell transplantation (HSCT), neutropenia, or malignancy [2, 3]. The incidence of mucormycosis appears to be increasing, based on data from cancer centers in the United States and Europe [2, 4–8] and PubMed publications [9]. Furthermore, a recent, comprehensive, population-based epidemiology study found a near doubling of the frequency of mucormycosis cases throughout France over a 10-year period (1997–2006) [10].

For decades, the mortality rate of mucormycosis has remained  $\geq 40\%$  despite aggressive surgical and antifungal therapy [2, 3, 7, 11–14]. In patients with hematologic malignancy or HSCT, mortality rates exceed 65% and 90%,

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respectively. Mortality rates exceed 65% in patients with hematologic malignancy, and in those with HSCT, mortality rates exceed 90%. However, recent translational research, funded by the US National Institutes of Health and by the pharmaceutical industry, has resulted in several new treatment strategies for mucormycosis, raising the possibility of improving outcomes based on superior medical therapy.

### Background Treatment Strategies for Mucormycosis

The successful treatment of mucormycosis requires four steps: 1) early diagnosis; 2) reversal of underlying predisposing risk factors, if possible; 3) surgical debridement where applicable; and 4) prompt antifungal therapy [3].

#### Early Diagnosis

A recent study from Chamilos et al. [15••] quantified the benefit of early initiation of polyene antifungal therapy. They reported that if treatment was initiated within 5 days of diagnosis of mucormycosis, survival was markedly improved compared to initiation of polyene therapy at  $\geq 6$  days after diagnosis (83% vs 49% survival). Hence, establishing an early diagnosis of mucormycosis is critical to enable early initiation of active antifungal therapy.

The development of other diagnostic methods is a major unmet need for this infection. Development of quantitative polymerase chain reaction systems is a promising area of ongoing research to enable more rapid diagnosis [16–19]. The most common finding by CT scanning of patients with rhino-orbital-cerebral disease is simply sinusitis, so absence of deeper infection by CT scan does not rule out mucormycosis [20••]. MRIs are more sensitive than CT scans for detecting orbital and central nervous system (CNS) involvement [20••]. CT scans are useful for early detection of pulmonary mucormycosis, particularly in patients with cancer. By logistic regression, pulmonary mucormycosis in patients with cancer could be distinguished from aspergillosis on the basis of sinusitis, presence of multiple ( $\geq 10$ ) nodules by CT scan, and pleural effusion [21].

#### Reversal of Underlying Disease

It is critical to reverse/prevent underlying defects in host defense when treating patients with mucormycosis. Immunosuppressive medications, particularly corticosteroids, should be dose reduced or stopped if at all possible. Aggressive management to rapidly restore euglycemia and normal acid-base status is critical in diabetic patients in ketoacidosis. Administration of iron should be avoided, because it exacerbates the severity of infection in animal models of

mucormycosis [22, 23, 24••]. For the same reason, it may be advisable to minimize blood transfusions, if feasible.

#### Surgical Management

Blood vessel thrombosis and resulting tissue necrosis during mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of necrotic tissues may be critical for complete eradication of mucormycosis. In a recent study, surgery was found to be an independent variable by logistic regression for favorable outcome in patients with mucormycosis [2]. Furthermore, in multiple case series, patients who did not undergo surgical debridement of mucormycosis had a far higher mortality rate than patients who underwent surgery [5, 25–32]. Although there is potential selection bias in these case series, as patients who did not undergo surgery likely differed in disease severity or comorbidities from those who did, these data support the concept that surgical debridement is necessary to optimize cure rates.

The extent and timing of surgical debridement necessary to maximize outcomes of mucormycosis has never been defined. Data from a recent retrospective review of patients with rhino-orbital-cerebral mucormycosis [20••] support the use of intraoperative frozen sections to delineate the margins of infected tissues so that uninvolved tissues can be spared from debridement. The use of calcofluor fluorescence microscopy has also been reported to increase the sensitivity of frozen sections for guiding extent of surgical revision [33].

#### Antifungal Therapy

##### First-Line Monotherapy Options

In general, primary antifungal therapy for mucormycosis should be based on a polyene, if possible. Although amphotericin B deoxycholate (AmB) was the cornerstone of mucormycosis therapy for decades, lipid formulations of AmB are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time than AmB [20••, 34]. Furthermore, treatment of mucormycosis with liposomal amphotericin B (LAmB) was associated with a 67% survival rate, compared to 39% survival when patients were treated with AmB ( $p=0.02$ ) [9]. Multiple other, more recent case series also found initial therapy with LAmB to be substantially more effective than other options [13, 35, 36]. Therefore, most experts now prefer to use lipid polyenes rather than AmB for the treatment of mucormycosis.

Available data indicate advantages of LAmB over amphotericin B lipid complex (ABLC) for the treatment

of CNS mucormycosis. For example, LAmB levels achieved in rabbit brain were fivefold above ABLC levels [37]. Furthermore, while similarly effective in neutropenic mice, LAmB was markedly superior to ABLC in diabetic ketoacidotic (DKA) mice infected with *Rhizopus oryzae*, primarily because of superior clearance of fungus from the brain [38]. These animal studies are complemented by a recent, relatively small retrospective case series, in which the outcomes of patients with rhino-orbital-cerebral mucormycosis were found to be worse when ABLC was used as initial therapy versus AmB or LAmB [20••].

In contrast, a recent murine study found that ABLC achieves superior lung levels than LAmB, resulting in superior clearance of fungus from the lungs [39]. When a higher dose of LAmB was used than ABLC, the efficacy was similar. No clinical studies are available yet to validate these intriguing murine data.

In the absence of definitive data on dose selection, 5–7.5 mg/kg/d of lipid polyenes are reasonable for most cases of mucormycosis. A recent randomized study of 339 patients with various mold infections found no clinical benefit of LAmB dosed at 10 mg/kg/d versus 3 mg/kg/d [40]. However, there were only five total cases of mucormycosis in the study, none of which involved the CNS. Given the low CNS penetration of polyenes, some experts prefer dose escalation to 10 mg/kg/d of LAmB for CNS mucormycosis. Higher doses of LAmB do not result in pharmacokinetic advantage compared to 10 mg/kg/d [41].

Fluconazole, voriconazole, and itraconazole do not have reliable activity against mucormycosis [42–52]. The reported in vitro minimum inhibitory concentration for 90% of organisms ( $MIC_{90}$ ) of posaconazole against the Mucormycotina has ranged from 1  $\mu\text{g}/\text{mL}$  to  $\geq 4 \mu\text{g}/\text{mL}$  [42, 53–56]. However, in patients with febrile neutropenia or invasive fungal infections, posaconazole dosed at 400 mg twice daily resulted in serum levels less than 1  $\mu\text{g}/\text{mL}$ , with considerable variability [57–59]. These data raise concerns about the reliability of achieving adequate in vivo levels of posaconazole to treat mucormycosis. Furthermore, posaconazole is relatively ineffective for the treatment of mucormycosis in pre-clinical animal models [50, 60–62]. The efficacy of posaconazole as a treatment option is further called into question by reports of mucormycosis developing as a breakthrough infection while on posaconazole prophylaxis [63–65]. Thus, posaconazole cannot be recommended as a first-line treatment for mucormycosis.

In contrast, van Burik et al. [66] reported 60% response rates (45% partial response, 15% complete response) for salvage therapy in patients with mucormycosis who were refractory to or intolerant of polyenes. Greenberg et al. [67] reported similar results. Hence, posaconazole is an option for salvage therapy for these infections.

## Combination Antifungal Therapy for Mucormycosis

It is now known that *R. oryzae* expresses the target enzyme for echinocandins [68]. In DKA mice infected with *R. oryzae*, combination caspofungin plus ABLC therapy markedly improved survival compared to either monotherapy or placebo [69]. Combination therapy with LAmB plus either micafungin or anidulafungin was also synergistic in either neutropenic or DKA mice with disseminated mucormycosis [70].

In a recent retrospective review from two institutions, combination polyene-caspofungin therapy was associated with significantly improved outcomes in patients with rhino-orbital and rhino-orbital-cerebral mucormycosis compared to polyene monotherapy [20••]. Most of the patients were diabetic, although some patients in the series had neutropenia or were solid-organ transplant recipients. In multivariate analysis, only combination therapy was significantly associated with superior outcomes (OR = 10.9 for success vs monotherapy,  $p=0.02$ ).

Echinocandins have extremely favorable toxicity profiles. Furthermore, at an average hospitalization cost of  $\sim \$100,000$  per case of mucormycosis [71], addition of an echinocandin at  $\sim \$100$  per day for 2–4 weeks would increase hospital costs by a small amount (ie,  $<3\%$ ). Thus, neither toxicity nor cost is a compelling reason to avoid combination polyene-echinocandin therapy for patients with mucormycosis. If used as combination therapy, echinocandins should be administered at standard doses—dose escalation is not recommended, due to paradoxical loss of efficacy during murine mucormycosis at doses  $\geq 3 \text{ mg}/\text{kg}/\text{d}$  [68, 70]. A large-scale, definitive, phase 3 clinical trial is necessary to determine if combination lipid polyene-echinocandin therapy is superior to monotherapy.

The central role of iron in pathogenesis of mucormycosis has been confirmed based on in vitro and in vivo animal models, and retrospective human studies [22, 23, 24••, 72–75, 76••]. The requirement for iron acquisition for *R. oryzae* growth and pathogenesis suggested that abrogation of iron uptake could be an important therapeutic adjunct for mucormycosis infections. Indeed, the iron chelators deferasiprone and deferasirox, the latter of which is approved by the US Food and Drug Administration to treat iron overload in transfusion-dependent anemias [77], improved survival in rodents with mucormycosis [24••, 72, 74]. Deferasirox was cidal for 28 of 29 clinical isolates of Mucormycotina in vitro, with an  $MIC_{90}$  of 6.25  $\mu\text{g}/\text{mL}$  [34••]. The drug exhibited time-dependent killing, with cidal activity occurring at 12–24 h of drug exposure. Based on trough serum levels of greater than 15  $\mu\text{g}/\text{mL}$  in patients treated with deferasirox at 20 mg/kg/d, it should be feasible to maintain serum levels in excess of the MICs of Mucormycotina throughout the entire dosing interval [78, 79].

In mice with disseminated mucormycosis, deferasirox was as effective as LAmB therapy, and combination deferasirox-LAmB therapy synergistically improved survival (80% survival for combination vs 40% for either monotherapy vs 0% for placebo) [24••]. In particular, combination therapy resulted in a 100-fold decrease in brain fungal burden compared to monotherapy. Based on these animal data, deferasirox has been used off label as adjunctive therapy for mucormycosis patients, both when it was the first agent prescribed temporally and in salvage situations [80, 81]. Although limited open-label clinical experience has not revealed substantial toxicity of the addition of deferasirox to a polyene or posaconazole-based backbone regimen, a recently completed phase 2, double-blind, randomized, placebo-controlled trial of adjunctive deferasirox therapy failed to demonstrate a benefit of the combination regimen in patients with mucormycosis.

The toxicities of deferasirox therapy in nonhuman primates and in clinical trials have been extensively reviewed [77, 82, 83], and are beyond the scope of the current article. However, the primary toxicity of concern for the treatment of mucormycosis is renal failure. Elevations in creatinine occurred in up to one third of patients in deferasirox clinical trials [82, 84], but were usually mild and almost always reversible upon cessation of the drug. There have been rare, postmarketing reports of severe acute renal failure resulting in hemodialysis or death in patients taking deferasirox [85]. However, these patients typically had other underlying risk factors for renal failure. Therefore, the contribution of deferasirox to the renal failure in these cases is unclear. Until more data are available, deferasirox should be used cautiously in the setting of mucormycosis, as toxicities are not well characterized.

No clinical data exist to address the role of combination posaconazole-polyene therapy for mucormycosis. However, two recent pre-clinical studies evaluated the efficacy of posaconazole combination therapy during murine mucormycosis. In the first study, Rodriguez et al. [61] found that combining posaconazole with AmB enhanced the survival of neutropenic mice infected with *R. oryzae* only when compared to a subtherapeutic dose of AmB monotherapy (0.3 mg/kg/d). In contrast, combination therapy was of no advantage compared to AmB monotherapy at a standard dose (0.8 mg/kg/d). Similarly, we recently reported that combination posaconazole plus LAmB was of no benefit compared to monotherapy with LAmB alone in either neutropenic or DKA mice with mucormycosis [62]. Based on available data, posaconazole does not have a clear role as adjunctive therapy in combination with lipid polyenes.

Ben-Ami et al. [86] recently reported that the antibacterial agent, colistin, has activity against the Mucorales. Colistin was cidal in vitro, although regrowth of the fungus occurred unless subinhibitory AmB was added for synergy. Colistin's

mechanism of action appeared to involve disruption of the cytoplasmic and intracellular vacuolar membrane integrity. The drug had limited activity as a prophylactic agent during inhalational challenge, but did not have systemic therapeutic activity. Its potential role as a second agent in a combination regimen merits further study.

Proinflammatory cytokines, such as interferon (IFN)- $\gamma$  and granulocyte-macrophage colony-stimulating factor (GM-CSF), enhance the ability of granulocytes to damage the agents of mucormycosis [87]. Adjunctive immune therapy with recombinant granulocyte colony-stimulating factor (G-CSF) and GM-CSF, or with recombinant IFN- $\gamma$ , has been used successfully in conjunction with lipid formulations of amphotericin B in treatment of mucormycosis [88–90]. Whether recombinant cytokines have a role in the primary treatment of mucormycosis in immunocompromised patients is not well-defined.

G-CSF-mobilized granulocyte transfusions have been increasingly used for refractory mycoses, including mucormycosis [91]. Although the reported experience in management of mucormycosis with granulocyte transfusions is limited, such transfusions use may contain the infection and be life-saving in persistently neutropenic hosts with this infection. Finally, based on limited experimental and clinical data, hyperbaric oxygen therapy may be also useful in centers with the appropriate technical expertise and facilities [92].

### Salvage Therapy

Posaconazole or deferasirox are reasonable salvage options for patients with mucormycosis refractory to or intolerant of polyene therapy. Substantially more clinical data are available for posaconazole in this setting [66, 67]. Posaconazole appears to be quite safe despite dosing for months to years of administration [66, 67].

Experience is limited with deferasirox as salvage therapy. However, in case series and case reports, its addition to patients progressing on previous therapy has resulted in favorable outcomes without substantive toxicity [80, 86, 93]. If deferasirox is used, it should be used cautiously and with regular monitoring of renal and hepatic function. Administration at a dose of 20 mg/kg/d for 2–4 weeks is reasonable for salvage therapy, because in pre-clinical studies of non-iron-overloaded primates, deferasirox toxicity increased beyond 4 weeks of therapy [83].

G-CSF-mobilized granulocyte transfusions may provide additional support for persistently neutropenic patients until recovery from neutropenia. Administration of GM-CSF or IFN- $\gamma$  may further augment host response and antifungal effect in non-neutropenic patients with refractory infection. In a recent murine study, addition to LAmB therapy of GM-



CSF, but not IFN- $\gamma$ , improved the survival of mice with mucormycosis [94].

## Conclusions

In recent years, numerous new options for the treatment of mucormycosis have become available. Lipid formulations of amphotericin are currently the preferred first-line treatment for mucormycosis, with a possible preference for liposomal amphotericin for CNS infection. The possibility of combination therapy with lipid amphotericin B and an echinocandins or iron-blocking strategy merits additional investigation. Salvage therapy options are numerous, including posaconazole, deferasirox, adjunctive cytokine therapy, and hyperbaric oxygen. Underlying all successful antifungal use is the need to reverse underlying host defects predisposing to infection, surgically debride necrotic tissue whenever possible, and make an early diagnosis to facilitate rapid initiation of antifungal therapy.

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