Recent Advances in the Management of Mucormycosis: From Bench to Bedside

Brad Spellberg,1,2 Thomas J. Walsh,3 Dimitrios P. Kontoyiannis,4 John Edwards, Jr.,1,2 and Ashraf S. Ibrahim1,2
1Division of Infectious Diseases, Los Angeles Biomedical Research Institute at Harbor–University of California at Los Angeles (UCLA) Medical Center, Torrance, and 2The David Geffen School of Medicine at UCLA, Los Angeles, California; 3National Cancer Institute, Bethesda, Maryland; and 4The University of Texas M. D. Anderson Cancer Center, Houston

Recent advances in the management of mucormycosis have the potential to improve outcomes of mucormycosis. Lipid formulations of amphotericin B (LFA) have evolved as the cornerstone of primary therapy for mucormycosis. Posaconazole may be useful as salvage therapy, but it cannot be recommended as primary therapy for mucormycosis on the basis of available data. Preclinical and limited retrospective clinical data suggest that combination LFA-echinocandin therapy may improve survival during mucormycosis. A definitive trial is needed to confirm these results. Combination therapy with LFA and the iron chelator, deferasirox, also improved outcomes in animal models of mucormycosis. In contrast, combination polyene-posaconazole therapy was of no benefit in preclinical studies. Adjunctive therapy with recombinant cytokines, hyperbaric oxygen, and/or granulocyte transfusions can be considered for selected patients. Early initiation of therapy is critical to maximizing outcomes; recent developments in polymerase chain reaction technology are advancing early diagnostic strategies. Prospective, randomized clinical trials are needed to define optimal management strategies for mucormycosis.

Mucormycosis is a life-threatening infection caused by fungi of the order Mucorales. Recent reclassification has abolished the order Zygomycetidae 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, patients who have received organ or hematopoietic stem cell transplant (HSCT), patients with neutropenia, or patients with malignancy [2, 3]. The incidence of mucormycosis appears to be increasing [4], particularly in certain oncology centers [2, 5–7]. For decades, the mortality rate of mucormycosis has remained ≥40% despite aggressive surgical and polyene antifungal therapy [2, 3, 8]. In particular, patients with hematologic malignancy or HSCT recipients have mortality rates in excess of 65% and 90%, respectively [2, 4, 6, 7]. However, as a result of recent translational research, funded by the US National Institutes of Health and industry, agents are now available to attack the Mucorales at multiple biochemical targets (figure 1). Here, we review treatment and diagnostic strategies for mucormycosis in the 21st century. We emphasize that these evolving management strategies are based on recent preclinical and limited, uncontrolled clinical data and that their validation requires definitive, prospective, controlled clinical trials.

ANTIFUNGAL AGENTS FOR MUCORMYCOSIS

Polyenes. Amphotericin B deoxycholate (AmB) remains the only licensed antifungal agent for the treatment of mucormycosis. However, lipid formulations of AmB (LFABs) are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time than AmB [9, 10]. In one study, amphotericin B lipid complex (ABLC) resulted in a 71% success rate as salvage therapy for mucormycosis [11]. Furthermore, treatment with liposomal amphotericin B (LAmB) was associated with a 67% survival rate (16 of 24 patients), compared with 39% survival (24 of 62 patients) with AmB (P = .02) among patients with cancer who experienced mucormycosis [4]. Thus, LFABs appear to be safer, efficacious alternatives to AmB for the treatment of mucormycosis (table 1).

Limited data suggest advantages of LAmB over ABLC for
Figure 1. Current targets of therapy for mucormycosis. As a result of recent translational research, strategies are available to attack 4 biochemical targets in Mucorales. These targets include (1) polyene binding to ergosterol in the cell membrane, resulting in creation of pores in the membrane; (2) posaconazole inhibition of cytochrome p450 14-α-demethylase, blocking synthesis of cell membrane-stabilizing ergosterol; (3) echinocandin inhibition of cross-linking of β-glucan in the fungal cell wall; and (4) deferasirox iron chelation therapy, blocking uptake of iron, which is essential for fungal growth. In addition, adjunctive therapy with host immune enhancing strategies, such as (5) granulocyte transfusions and (6) cytokine therapy, are possible. Granulocytes can damage the fungal cell and can be activated by recombinant cytokines, including granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), and interferon-γ (IFN-γ). Polymorphonuclear leukocytes also can be delivered to the site of infection in neutropenic hosts by granulocyte transfusions. Polymorphonuclear leukocytes and lipid formulations of amphotericin B act synergistically to damage hyphae of Rhizopus species.

treating central nervous system mucormycosis. Specifically, LAmB levels in rabbit brain were ~5-fold above ABLC levels [12]. Furthermore, although LAmB and ABLC were similarly effective among neutropenic mice, LAmB was superior to ABLC when administered in identical dosages to diabetic ketoacidotic (DKA) mice infected with Rhizopus oryzae, primarily because of superior clearance of fungus from the brain [22]. These animal studies are complemented by a recent, retrospective series in which the outcomes of patients with rhino-orbital-cerebral mucormycosis were inferior when ABLC was used as primary therapy, compared with either AmB or LAmB [9].

The response of mucormycosis to antifungal agents is host and site dependent and is particularly problematic in patients with hematological disorders and HSCT recipients [2]. For example, Shoham et al. [23] recently reported a 32% response rate to LAmB as primary therapy for mucormycosis in 32 patients with hematological malignancies and pulmonary infections. Thus, host-dependent variation in response should be considered in prognosis and management of patients with mucormycosis and in designing clinical trials for the disease.

**Azoles.** Fluconazole and voriconazole do not have reliable activity against the agents of mucormycosis, and the activity of itraconazole is primarily limited to Absidia species [24–34]. In contrast, posaconazole has enhanced in vitro activity against the Mucorales, with reported 90% minimum inhibitory concentrations (MIC90) of 1 to ≥ 4 μg/mL [24, 35–38]. However, among febrile patients with neutropenia or those with invasive fungal infection, posaconazole administered at a dosage of 400 mg orally twice daily resulted in serum levels <1 μg/mL, with considerable variability [39–41]. Although such levels may result in favorable outcome in the treatment of invasive aspergillosis [42], the MICs of Aspergillus fumigatus are consistently <0.5 μg/mL [43]. Therefore, pharmacokinetic and pharmacodynamic data raise concerns about the reliability of achieving adequate in vivo levels of oral posaconazole to treat mucormycosis, in contrast to aspergillosis. As a result, therapeutic drug monitoring may be warranted during treatment of mucormycosis with posaconazole, particularly among patients at high risk for malabsorption (e.g., patients with mucositis and patients with gastrointestinal graft-versus-host disease) [44].

Furthermore, data from murine models of mucormycosis (in which serum posaconazole levels are ≥5 μg/mL [45]) raise further concerns about the efficacy of posaconazole for mucormycosis. In neutropenic mice infected with Mucor species, Sun et al. [46] found that posaconazole was statistically significantly less effective than was AmB. Similarly, Dannaoui et al. [32] found that posaconazole was less effective than AmB in treating mice infected with Rhizopus microsporus or Absidia
Table 1. First-line antifungal options for mucormycosis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dosage</th>
<th>Advantages and supporting studies</th>
<th>Disadvantages</th>
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<tr>
<td><strong>Primary antifungal therapy</strong></td>
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<tr>
<td>AmB</td>
<td>1.0–1.5 mg/kg/day</td>
<td>&gt;5 decades clinical experience; inexpensive; only licensed agent for the treatment of mucormycosis</td>
<td>Highly toxic; poor CNS penetration</td>
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<tr>
<td>LAmB</td>
<td>5–10 mg/kg/day</td>
<td>Less nephrotoxic than AmB; better CNS penetration than AmB and ABLC [12]; improved outcomes vs. AmB in murine models and a retrospective clinical review [4, 13]</td>
<td>Expensive</td>
</tr>
<tr>
<td>ABLC</td>
<td>5–7.5 mg/kg/d</td>
<td>Less nephrotoxic than AmB; murine and retrospective clinical data suggest benefit of combination therapy with echinocandins [9, 14]</td>
<td>More nephrotoxic than LAmB [15]; possibly less efficacious than other options as monotherapy, particularly for CNS infection [9]</td>
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<tr>
<td><strong>Primary combination therapy</strong></td>
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<tr>
<td>Caspofungin plus lipid polyene</td>
<td>70 mg iv load, then 50 mg/day for ≥2 weeks; 50 mg/m² iv for children [16]</td>
<td>Favorable toxicity profile; synergistic in murine disseminated mucormycosis [14]; retrospective clinical data suggested superior outcomes with combination caspofungin-lipid polyene therapy for rhino-orbital-cerebral mucormycosis [9]</td>
<td>Clinical data of combination therapy are very limited</td>
</tr>
<tr>
<td>Micafungin OR anidulafungin plus lipid polyene</td>
<td>100 mg/day for ≥2 weeks; micafungin 4 mg/kg/day for children [17]; micafungin 10 mg/kg/day for low-birth weight infants [18]; anidulafungin 1.5 mg/kg/day for children [19]</td>
<td>Favorable toxicity profile; synergistic with LAmB in murine model of disseminated mucormycosis [20]</td>
<td>No clinical data</td>
</tr>
<tr>
<td>Deferasirox plus lipid polyene</td>
<td>20 mg/kg po qd for 2–4 weeks</td>
<td>Highly fungicidal for Mucorales in vitro [21]; synergistic with LAmB in murine model of disseminated mucormycosis [21]</td>
<td>Only available for enteral administration; no clinical data, although a phase II clinical trial is ongoing</td>
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</table>

NOTE. Primary therapy should generally include a polyene. Non-polyene-based regimens may be appropriate for patients who refuse polyene therapy or for patients with mild disease in relatively immunocompetent hosts that can be surgically eradicated (e.g., isolated suprafascial cutaneous infection). ABLC, amphotericin B lipid complex; AmB, amphotericin B deoxycholate; CNS, central nervous system; iv, intravenous; LAmB, liposomal amphotericin B; po, oral; qd, once per day.

* Prospective, randomized trials are necessary to confirm the suggestion of benefit of combination therapy from animal and small, retrospective human studies of mucormycosis. Also, increasing the dosage of any of the echinocandins is not recommended based on paradoxical loss of benefit of combination therapy at echinocandin dosages of ≥3 mg/kg/d.
species. In addition, they found that posaconazole was no better than placebo for treating \textit{R. oryzae}, which causes $>$70\% of clinical cases of mucormycosis \cite{2, 3, 9}. Finally, in 2 more recent studies, posaconazole monotherapy was also no better than placebo for the treatment of \textit{R. oryzae} infection in neutropenic or DKA mice \cite{47, 48}. Thus, data from 4 groups of investigators indicated that posaconazole was inferior in efficacy to LAmB for the treatment of murine mucormycosis, and 3 groups found that it was not superior to placebo for treating mice infected with \textit{R. oryzae}.

On the basis of the available animal data and the absence of clinical data, posaconazole monotherapy cannot be recommended as primary treatment of mucormycosis. In contrast, available clinical data from open-label salvage studies suggest that posaconazole is a reasonable option for patients with mucormycosis who are refractory to or intolerant of polyenes \cite{49, 50}.

**Combination Antifungal Therapy for Mucormycosis**

**Echinocandins.** \textit{R. oryzae} expresses the target enzyme for echinocandins \cite{51}, and in DKA mice infected with \textit{R. oryzae}, combination caspofungin plus ABLC therapy markedly improved survival, compared with monotherapy or placebo \cite{14}. Combination therapy with LAmB plus either micafungin or anidulafungin also improved outcome in neutropenic and DKA mice with disseminated mucormycosis \cite{20}. Enhanced exposure of $b$-glucan on the fungal surface, which results in immune stimulation, may be one of the mechanisms by which echinocandins improve outcomes in mucormycosis \cite{52}.

In a recent, small, retrospective study, combination LFAB-caspofungin therapy was associated with significantly improved outcomes for rhino-orbital-cerebral mucormycosis among patients with diabetes, compared with polyene monotherapy \cite{9}. By multivariate analysis, only combination therapy was significantly associated with superior outcomes (odds ratio, 10.9 for success vs. monotherapy; $P = .02$). We emphasize that these data require confirmation in a prospective, randomized trial. In the meantime, if combination LFAB-echinocandin therapy is considered for mucormycosis, echinocandins should be administered at US Food and Drug Administration–approved dosages (table 1). Increasing the dosage of the echinocandins is not advisable because of a paradoxical loss of efficacy against murine mucormycosis at dosages $\geq 3$ mg/kg/day \cite{51, 20}.

**Iron chelation therapy.** Deferoxamine iron chelation therapy predisposes to mucormycosis \cite{53}, because deferoxamine actually enhances delivery of iron to Mucorales \cite{54, 55}. Indeed, animals infected with \textit{R. oryzae} that are treated with iron or deferoxamine have markedly worse survival than do animals treated with placebo \cite{54–56}. However, other iron chelators cannot be used by Mucorales to acquire iron \cite{53, 54, 56}. In 2005, a new orally available iron chelator, deferasirox, was approved by the US Food and Drug Administration for the treatment of iron overload among patients with transfusion-dependent anemia \cite{57}. Deferasirox was fungicidal for clinical isolates of Mucorales in vitro, with an MIC$_{90}$ of 6.25 $\mu$g/mL \cite{21}. The drug exhibited time-dependent killing, with cidalty occurring at 12–24 h of drug exposure. Based on trough serum levels $>$15 $\mu$g/mL in patients who are treated with deferasirox at 20 mg/kg/day \cite{58, 59}, it should be feasible to maintain deferasirox serum levels in excess of the MICs of Mucorales.

In DKA 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 monotherapy vs. 0\% for placebo) \cite{21}. In particular, combination therapy resulted in a 100-fold decrease in brain fungal burden, compared with monotherapy. On the basis of these animal data, we successfully used deferasirox as salvage therapy for a patient with advanced rhinocerebral mucormycosis who had progressive brainstem disease despite having received LAmB therapy \cite{60}. Currently, a double-blinded, randomized, placebo-controlled, phase II safety/exploratory efficacy study of adjunctive deferasirox therapy (20 mg/kg/day for 14 days) for mucormycosis is ongoing (the Deferasirox-AmBisome Therapy for Mucormycosis—or DEFEAT Mucor—study [NCT00419770]).

Soummer et al. \cite{61} recently reported the failure of salvage deferasirox for a patient who had undergone partial colectomy to resect mucormycosis. Although its intravenous formulation is under active clinical development \cite{62}, deferasirox, like posaconazole, is currently only available in oral formulation. Therefore, patients who are not likely to adequately absorb enteral medications (e.g., patients who have undergone intestinal surgery) should not be treated with deferasirox.

The toxicities of deferasirox therapy in nonhuman primates and in clinical trials have been extensively reviewed \cite{57, 63, 64} and are beyond the scope of this article. Gastrointestinal symptoms (e.g., nausea and diarrhea) are the most common adverse effects of deferasirox therapy. However, the primary toxicity of concern is renal. Elevations in creatinine occurred in up to one-third of patients in deferasirox clinical trials \cite{63, 65}, but they were usually mild and reversible upon cessation of drug use. There have been rare postmarketing reports of severe acute renal failure resulting in hemodialysis for or death of iron-overloaded patients receiving deferasirox \cite{66}. 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.

**Posaconazole combination therapy.** Two recent preclinical studies evaluated the efficacy of posaconazole combination therapy for murine mucormycosis. In the first study, Rodriguez et al. \cite{47} found that combining posaconazole with AmB en-
hanced the survival of neutropenic mice infected with R. oryzae only when compared to a subtherapeutic dosage (0.3 mg/kg/day) of AmB monotherapy. In contrast, combination therapy was of no advantage, compared with a standard dosage of AmB monotherapy (0.8 mg/kg/d). Similarly, we recently reported that combination posaconazole plus LAmB did not improve survival, compared with LAmB monotherapy, in either neutropenic or DKA mice with mucormycosis [48]. No clinical studies have evaluated combination posaconazole-polyene therapy for mucormycosis.

**Other adjunctive therapies.** Proinflammatory cytokines, such as interferon-γ and granulocyte macrophage colony-stimulating factor, enhance the ability of granulocytes to damage the agents of mucormycosis [67]. Case reports have described survival of patients with mucormycosis treated with adjunctive immune therapy with recombinant granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor, or with recombinant interferon-γ, in conjunction with LFAB [68–72]. The role of recombinant cytokines in the primary treatment of mucormycosis is not defined.

Granulocyte colony-stimulating factor–mobilized granulocyte transfusions have been increasingly used for refractory mycoses, including mucormycosis [73, 74]. Although the reported experience with granulocyte transfusions is limited, such transfusions may be life-saving for persistently neutropenic patients with mucormycosis. Finally, limited data indicate that hyperbaric oxygen may also be useful in health care centers with the appropriate technical expertise and facilities [75].

**SUGGESTED TREATMENT STRATEGIES FOR MUCORMYCOSIS**

**General principles.** The successful treatment of mucormycosis requires 4 steps: (1) early diagnosis; (2) reversal of underlying predisposing risk factors, if possible; (3) surgical debridement where applicable; and (4) prompt antifungal therapy [3]. We will review each of these principles in the context of recent advances in the treatment of mucormycosis.

**Early diagnosis of mucormycosis.** Initiation of polyene therapy within 5 days after diagnosis of mucormycosis was associated with improvement in survival, compared with initiation of polyene therapy at ≥6 days after diagnosis (83% vs. 49% survival) [76]. Therefore, establishing an early diagnosis of mucormycosis is critical to enable early initiation of active antifungal therapy.

Although some progress has been made in improving the laboratory yield of cultures for mucormycosis [77], 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 [78, 79]. For example, Kasai et al. [80] developed 2 real-time quantitative polymerase chain reaction assays that targeted the 28S rRNA gene for the diagnosis of mucormycosis caused by Rhizopus, Mucor, and Cunninghamella species. These polymerase chain reaction assays successfully detected circulating DNA in rabbits with experimental pulmonary mucormycosis. A prospective clinical study of molecular detection of pulmonary mucormycosis is currently being developed.

Among patients with rhino-orbital-cerebral disease, computed tomography typically reveals only sinusitis, so computed tomography that indicates the absence of deeper infection does not rule out mucormycosis [9]. Magnetic resonance imaging is more sensitive than computed tomography for detecting orbital and central nervous system involvement [9]. Computed tomography is 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 (≥10) nodules on computed tomography, and pleural effusion [81]. Also, a recent retrospective study reported that 7 of 8 immunocompromised patients treated at a cancer center who had a reverse halo sign (focal area of ground-glass attenuation surrounded by a ring of consolidation) on chest computed tomography had mucormycosis, rather than other molds [82]. The reverse halo sign was seen early in the disease course of these patients. Further refinement of radiographic techniques for distinguishing mucormycosis from other infectious and noninfectious diseases is an important area of future research.

**Reversal of underlying disease.** It is critical to reverse or prevent underlying defects in host defense when treating patients with mucormycosis. Immunosuppressive medications, particularly corticosteroids, should be administered at reduced dosages or stopped if at all possible. Aggressive treatment to rapidly restore euglycemia and normal acid-base status is critical in diabetics in ketoacidosis.

**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 logistic regression model, surgery was found to be an independent variable for favorable outcome among 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 did patients who underwent surgery [6, 83–90]. Although there is potential selection bias in these case series, because 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. Limited data from a retrospective review of patients with rhino-orbital-cerebral mucormycosis [9] support the concept of an “aggressive-conservative” approach, in which intraoperative frozen sections are used to delineate the margins of infected tissues, and uninvolved tissues are spared from debridement when possible.

**Primary antifungal therapy.** Primary antifungal therapy for mucormycosis should be based on a polypene in most cases, unless patients refuse polypene therapy or, possibly, in cases of milder infection in relatively immunocompetent hosts for whom surgical eradication of disease has been accomplished (e.g., cases of isolated, suprafascial cutaneous infection) (table 1). The optimal dosages for treatment of mucormycosis are not known for any antifungal agent. Starting dosages of 1 mg/kg/day for AmB and 5–7.5 mg/kg/day for LAMB and ABLC are commonly used for adults and children. Whether higher dosages provide any additional benefit is uncertain. However, increasing the dosage of LAMB to 10 mg/kg/day for central nervous system mucormycosis may be considered on the basis of the limited polyene penetration into the brain. Higher dosages of LAMB do not result in pharmacokinetic advantage compared with a dosage of 10 mg/kg/day [91].

The role of combination therapy as primary treatment for mucormycosis has been the subject of a recent review, which concluded that the available data are insufficient to support a general recommendation [92]. As described above, limited data from mice [14, 20] and diabetic patients [9] suggest that combination echinocandin-LFAB therapy may be a reasonable strategy for treating mucormycosis, but these results require a confirmatory, prospective, randomized study.

Based on the lack of efficacy in animal models and the lack of available clinical data, primary combination therapy with LFAB plus posaconazole cannot currently be recommended. In contrast, preclinical data support the addition of deferasirox to initial LFAB therapy, particularly for central nervous system infection in diabetic patients. The ongoing phase II, DEFEAT Mucor clinical trial should clarify the safety profile of initial LFAB-deferasirox combination therapy. Ultimately, prospective, randomized phase III clinical trials will be required to determine whether any combination therapeutic regimen is superior to monotherapy with an LFAB.

**Salvage therapy.** Deferasirox or posaconazole are reasonable salvage options for patients with mucormycosis refractory to or intolerant of polypene therapy (table 2). Substantially more clinical data are available for posaconazole in this setting [49, 50]. If deferasirox is used, it should be administered for 2–4 weeks during salvage therapy, because in preclinical studies of non–iron-overloaded primates, deferasirox toxicity increased beyond 4 weeks of therapy [64]. In contrast, posaconazole appears to be quite safe, despite dosing for months to years [49, 50].

Granulocyte colony-stimulating factor–mobilized granulocyte transusions may provide additional support for persistently neutropenic patients until recovery from neutropenia. Administration of granulocyte macrophage colony-stimulating factor or interferon-γ may further augment host response and antifungal effect in nonneutropenic patients with refractory infection.

**Total duration of therapy.** In the absence of comparative data, the total duration of therapy for mucormycosis should be individualized for each patient. In general, antifungal therapy for mucormycosis should be continued until all of the following objectives are attained: (1) there is resolution of clinical signs and symptoms of infection, (2) there is resolution or stabilization of residual radiographic signs of disease on serial im-

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<tr>
<th>Drug</th>
<th>Recommended dosage</th>
<th>Advantages and supporting studies</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Posaconazole with or without lipid polyenes</td>
<td>200 mg po qid or 400 mg po bid</td>
<td>Convenient oral dosing of posaconazole; retrospective case series demonstrated 60%–70% “success” rates (complete plus partial response) [49, 50]</td>
<td>Monotherapy posaconazole efficacy less than polyenes in murine studies [32, 46, 47, 93]; combination posaconazole plus LFAB no better than LFAB alone in murine studies</td>
</tr>
<tr>
<td>Deferasirox plus lipid polyenes</td>
<td>20 mg/kg po qid for 2–4 weeks</td>
<td>Convenient oral dosing of deferasirox; success in case report [60]</td>
<td>Limited published data</td>
</tr>
<tr>
<td>Granulocyte transfusions (for persistently neutropenic patients)</td>
<td>~10^9 cells/kg</td>
<td>Neutrophils and ABLC interact synergistically against Mucorales in vitro [96]; case reports of patients supported with granulocyte transusions [73, 74]</td>
<td>Limited clinical data; infusion related toxicity and alloimmunization</td>
</tr>
<tr>
<td>Recombinant cytokines G-CSF, GM-CSF, or IFN-γ</td>
<td>Dose G-CSF at 5 μg/kg/day; GM-CSF at 100–250 μg/m²; IFN-γ at 50 μg/m² for those with body surface area &gt;0.5 m² and 1.5 μg/kg for those with body surface area &lt;0.5 m²</td>
<td>In vitro studies demonstrate augmented host response of PMNs to hyphal elements of Rhizopus species [67]; individual case reports [68–72]</td>
<td>Limited clinical data</td>
</tr>
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</table>

NOTE. ABLC, amphotericin B lipid complex; bid, twice per day; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; PMNs, polymorphonuclear leukocyte; po, oral; qd, once per day.

*Outpatient deferasirox therapy currently requires enrollment in the Exjade Patient Assistance and Support Services (EPASS) system [94]. Inpatient therapy does not require EPASS enrollment.*
aging, and (3) there is resolution of underlying immunosuppression. Such a case is illustrated in a patient with lymphoma and renal mucormycosis [96].

For patients with mucormycosis who are receiving immunosuppressive medications, secondary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is continued. Posaconazole may be an option if polyenes cannot be used for prolonged periods. For patients with intermittent immunosuppression, such as those receiving intermittent cycles of chemotherapy who have adequate leukocyte counts between cycles, secondary prophylaxis should be reinitiated during neutropenia and should continue until the recovery from neutropenia.

FUTURE DIRECTIONS

Unmet needs for improved diagnosis, treatment, and prevention of mucormycosis remain formidable. New radiographic, molecular, and antigenic tools are required to improve early detection and therapeutic monitoring. New antifungal agents and combinations of existing agents should be further explored in the laboratory and in clinical trials. Designing informative clinical trials to address this uncommon but frequently lethal infection is a challenge that will require innovative strategies. Definitive clinical data from prospective randomized studies are required to allow refinement and a stronger basis for therapeutic recommendations. Finally, an understanding of the basic molecular, metabolic, and immunological properties of these organisms is paramount to advancing our understanding of mucormycosis.

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