Mucormycosis

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KEYWORDS

• Mucorales • Mucormycosis • Diabetes mellitus • Immunocompromised host

KEY POINTS

- Mucormycosis is a rare but aggressive fungal disease that mainly affects patients with poorly controlled diabetes mellitus and those who are severely immunocompromised, including patients with hematological malignancies and solid organ transplant recipients.
- Early recognition of infection is critical for treatment success, followed by prompt initiation of antifungal therapy with lipid formulation amphotericin B. Posaconazole and isavuconazole should be used for stepdown and salvage therapy.
- Surgical debridement is key, both for tissue diagnosis and for treatment, and should be pursued without delay whenever possible.
- In addition to surgery and antifungal therapy, reverting the underlying risk factor for infection is important for treatment response.

INTRODUCTION

Invasive mucormycosis is a life-threatening fungal infection that most frequently occurs in patients with underlying comorbidities impacting immune system function.[1–4] Rhino-orbital-cerebral involvement is most frequently seen in those with poorly controlled diabetes mellitus, whereas immunocompromised patients (including those with hematological malignancies and transplant recipients) frequently present with pulmonary involvement and disseminated infection.[3,5,6]

Even with advances in microbiologic tools and antifungal therapies, many challenges remain in both the diagnosis and the treatment of mucormycosis. A multifaceted approach, including the elimination of predisposing factors, aggressive surgical debridement, and effective antifungal therapy, is critical to improve patient survival. However, despite these interventions, the outcome of invasive mucormycosis remains ominous.[2,3]

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MICROBIOLOGY

Mucormycosis refers to infections caused by members of the order Mucorales. Although most human infections are caused by *Rhizopus*, *Mucor*, and *Rhizomucor*, other clinically relevant organisms within the order Mucorales include *Actinomucor*, *Apophysomyces*, *Cunninghamella*, *Lichtheimia* (previously named *Absidia*), *Saksenaea*, and *Syncephalastrum*.[7]

Fungi of the order Mucorales have unique features that distinguish them from other clinically relevant fungi, such as *Aspergillus* spp. First, Mucorales do not form true conidia (**Fig. 1**). Instead, Mucorales produce unicelled asexual spores (sporangiospores) endogenously without the involvement of preexisting cell walls.[7] In addition, Mucorales hyphae are broad, ribbonlike, multinucleated cells with none to rare septation (coenocytic hyphae). These hyphae typically develop from the germinal tube by apical extension and during tissue invasion may occasionally septate to delimit reproductive structures or swollen areas.[8] Occasional irregular branching may occur, representing a departure from apical growth related to nutrient resources in the cell wall (**Fig. 2**). In contrast, *Aspergillus* forms true conidia, and hyphae growth occurs in an isotropic fashion during germination. During this process, as the hyphae continue to grow apically, additional polarity axes enable septa formation (using the internal cellular wall) and lateral branching at regular intervals (see **Fig. 2**).[8,9]

EPIDEMIOLOGY AND HOST FACTORS

Mucorales are ubiquitous fungi usually found in soil, decaying organic matter, compost, and contaminated foods. Mucormycosis is considered a rare infection: diabetes remains the most prominent underlying medical comorbidity in infected patients, and was identified as an independent risk factor for rhino-orbital-cerebral mucormycosis in a meta-analysis of 851 cases.[3,6,10] However, over the last 2 decades, the number of cases reported in vulnerable patients with underlying immunosuppression (either innate or acquired) has increased.[11,12] The reason behind this increase remains unclear, but it is likely multifactorial, related to the increased use of immunosuppressant drugs, improvement in fungal diagnostics, and selection by the widespread use of voriconazole prophylaxis.[3,10,13] Patients with hematologic malignancies (particularly those with prolonged neutropenia) and hematopoietic stem cell

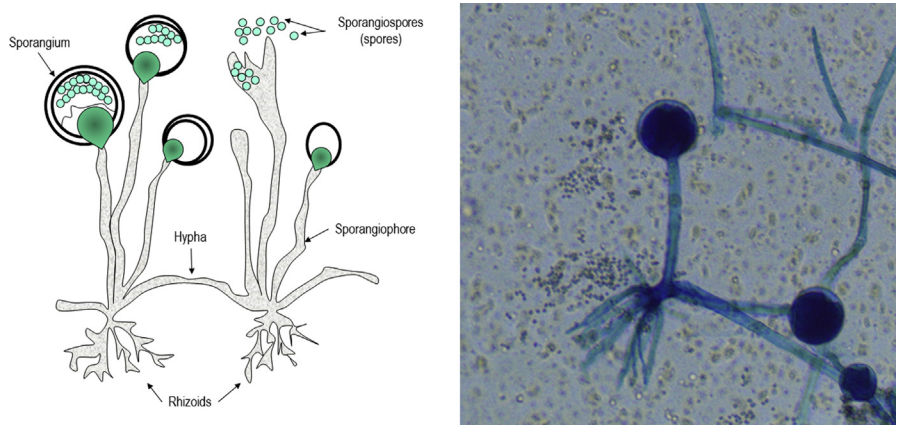


Fig. 1. Structure of *Rhizopus* species.

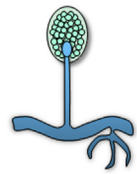
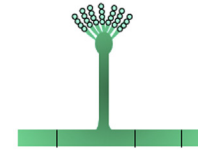
Feature	Mucorales	*Aspergillus* species
Asexual germination	Sporangiospores 	Conidia 
Hyphae	Coenocytic hyphae 	Septate hyphae 
Branching	Occasional and irregular 	Regular (acute angle) 

Fig. 2. Distinctive features of Mucorales versus *Aspergillus* species.

transplant recipients appear to become infected at higher rates than solid organ transplant recipients, particularly among those receiving treatment for graft-versus-host disease.[10,11,14–20] Cases of mucormycosis have also been linked to direct inoculation in the setting of trauma (primarily for cutaneous infection), iron overload, intravenous drug use, and malnourishment, even in the absence of diabetes and immunosuppression.[3,21–23] Health care–associated outbreaks of mucormycosis (from infected laundry, bandages, hospital construction) or infection in the setting of natural disasters has also been described.[24–28]

PATHOGENESIS

Fungal spores enter the respiratory tract through inhalation, enter the skin through direct inoculation to areas of trauma, or are ingested through the gastrointestinal tract.[29] Following initial entry, spores germinate into hyphae, resulting in angioinvasion with the potential for hematogenous dissemination and multiorgan involvement. Key virulence factors specific to the pathogenesis of Mucorales include the high-affinity iron permease (FTR1), which allows pathogen survival in iron-poor environments.[30,31] The spore coat (CotH) protein is present on the spore surface of Mucorales and impairs host immune defenses,[32] whereas the ADP-ribosylation factor appears to have a role in Mucorales growth and morphology.[33] Further research is needed to fully detail the effects of these and additional Mucorales virulence factors, including alkaline *Rhizopus* protease enzyme, calcineurin, and serine and aspartate proteases, to allow fungi to survive and invade the host.

Underlying host factors that impair immune system function can also contribute to the aggressive nature of mucormycosis infection. For instance, glucocorticoids are known to impair macrophage function, leading to infection progression and invasive

disease.[34] Hyperglycemia, acidosis, and iron overload have also been found to play an important role in the pathogenesis of Mucorales.[2,35]

In addition to factors attributable to the fungi and the host, external influences can also play a significant role in infection. It has been suggested that some of the toxins responsible for endothelial disruption may not be directly produced by the fungus itself, but rather as a result of bacterial endosymbiosis enhancing fungal virulence.[36,37] Voriconazole exposure has also been shown to augment the growth and virulence of Mucorales beyond selective pressure, but the exact mechanisms remain unknown.[38,39] Further studies are necessary to better understand the intricate mechanisms involved in the fascinating pathogenesis of Mucorales.

CLINICAL PRESENTATION

Individuals with mucormycosis can have diverse clinical manifestations contingent on the immune status of the host, the extent of the infection, and the involved organs. The most common and distinct presentation is rhino-orbital-cerebral infection, which typically occurs when fungal spores are inhaled into the sinuses. From there, the infection can remain localized, with symptoms consistent with acute sinusitis along with fever, headache, sinus pain, and nasal congestion. In vulnerable hosts, however, progression of the infection with invasion of the orbit and palate and further extension to the brain may occur. Local tissue invasion can result in several significant clinical abnormalities, including vision loss, cranial nerve palsies, and changes in mental status.[40] Rhino-orbital-cerebral mucormycosis is the most frequent presentation among patients with diabetes mellitus and hyperglycemia, particularly with ketoacidosis, and has also been reported in about one-third of solid organ transplant recipients with mucormycosis.[3–6,10,41,42] Rarely, this syndrome may occur in the absence of clear immunocompromising risk factors.[43] Clinical progression and invasive infection typically occur rapidly over days without appropriate treatment, although more protracted courses over weeks to months have been reported.[44] Rhino-orbital-cerebral mucormycosis has been reported to have a 25% to 62% mortality, without significant improvement in survival over the past 20 years, despite earlier and more aggressive medical and surgical therapy.[3–5,45,46] Of note, central nervous system infection can also occur without sinus involvement and direct extension. Central nervous system infection is thought to be secondary to hematogenous seeding and is more frequently seen in patients with a history of intravenous drug use or AIDS.[47,48]

Mucormycosis can also present with pulmonary infection after spore inhalation. Pulmonary infection is more common among patients with neutropenia owing to hematologic malignancies or recipients of hematopoietic stem cell or solid organ transplants.[3,16,42,49] Fever, chest pain, dyspnea, and hemoptysis (potentially massive and fatal) are often seen, owing to hyphal invasion of blood vessels and subsequent hemorrhage. Contiguous spread of this aggressive infection can lead to involvement of surrounding tissues, including bronchi, cardiac involvement, and mediastinitis.[50,51] The mortality of pulmonary mucormycosis has been reported between 48% and 87%.[3,5,15,16,19]

Cutaneous mucormycosis can be seen in both immunocompetent and immunocompromised patients but is the form of infection least likely to be associated with an underlying illness. As many as 50% of cases do not have overt immunosuppression but have undergone major antecedent trauma.[24–26,52] Infection can remain localized or extend to deeper structures, including surrounding bones, muscles, and tendons. It is less frequently seen as a component of disseminated infection.[53] Lesions start with painful erythema and induration and progressively become

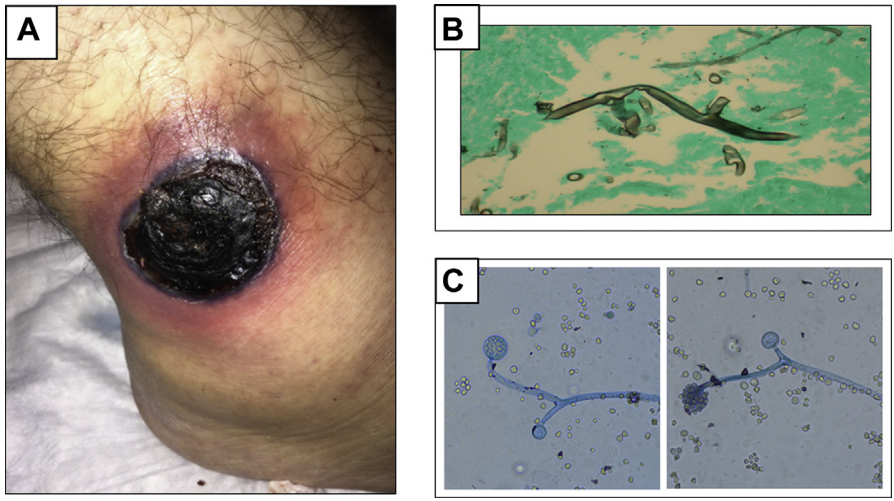


Fig. 3. Expanding and necrotic wound secondary to trauma in a 32-year-old man with relapsed acute lymphocytic leukemia on chemotherapy (*A*). Angioinvasive fungal hyphae with fibrinoid necrosis was demonstrated in skin biopsy (*B*). Cultures grew *Mucor* species (courtesy of Stephanie Agozino, MLS (ASCP), Michigan Medicine, Ann Arbor, MI) (*C*).

necrotic as they evolve over several days (Fig. 3), often with progression to necrotizing fasciitis (Fig. 4). Mortality is lower (~25%) than that noted in other forms of mucormycosis.[5]

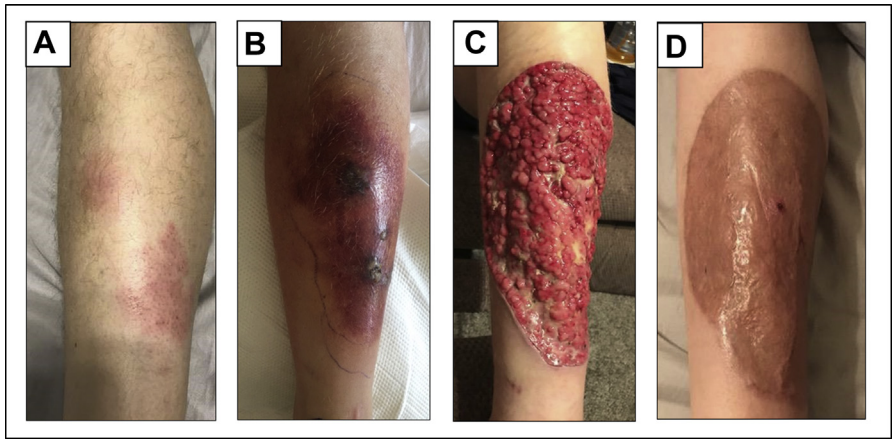


Fig. 4. A 23-year-old man with stage IV nodular sclerosing Hodgkin lymphoma presenting with erythema on his left leg in the setting of neutropenia after receiving chemotherapy (*A*). Within 24 hours, he developed fever and worsening pain and erythema and swelling with several discrete areas of necrosis with hemorrhage (*B*). Invasive mucormycosis was confirmed by urgent skin biopsy. The patient underwent extensive surgical debridement (*C*) followed by split-thickness skin grafting for closure of the surgical defect (*D*). In addition, he was treated with a prolonged course of IV L-AmB followed by stepdown posaconazole therapy throughout his remaining cycles of chemotherapy. He ultimately achieved remission, without recurrence of the fungal infection.

There are also more rare forms of disease. Gastrointestinal mucormycosis has been reported, thought to be secondary to spore ingestion. Gastrointestinal mucormycosis can involve multiple components of the gastrointestinal tract, including gastric ulceration of the stomach and intestinal involvement, including bowel perforation.[3,54–56] Many patients initially present with gastrointestinal bleeding. Renal mucormycosis has also been reported in increased frequency in patients with a history of intravenous drug use and AIDS.[57,58] It is thought to stem from hematogenous seeding during bloodstream fungal infection, similar to central nervous system infection.

Disseminated mucormycosis is seen in patients with significant immunocompromise. In one systematic review of 67 cases of mucormycosis in patients with human immunodeficiency virus, the most common presentation was disseminated infection, at 20%.[59] This presentation has the highest reported mortality at 96% despite appropriate treatment.[3]

DIAGNOSIS

Early diagnosis of mucormycosis is key to rapid and appropriate treatment and improved outcomes. The diagnosis of mucormycosis requires demonstration of characteristic wide, ribbonlike, nonseptate hyphae invading tissues on histopathology, accompanied by culture growth from specimens of involved sites.[60,61] Pathogen identification and antifungal susceptibilities are critical to determine appropriate antifungal therapy. However, it is not unusual that specimens are not sent for culture or that organisms do not grow. In such instances, diagnosis is made from histopathology alone, leading to significant limitations in the management of this disease.[61]

Radiographic findings alone are nonspecific and are usually insufficient for complete and accurate diagnosis of mucormycosis. Pulmonary infection has a spectrum of nonspecific radiographic appearances, similar to other fungal pneumonias, particularly aspergillosis.[61] Several computed tomographic (CT) findings, namely pleural effusion and multiple pulmonary nodules, along with clinical evidence of sinusitis, point toward mucormycosis as opposed to other fungi, particularly in the presence of an immunocompromised host.[62] The "reverse halo" sign has also been frequently reported, more commonly in pulmonary mucormycosis than in aspergillosis.[63,64] The reverse halo sign presents as a central ground glass opacification surrounded by a consolidative ring, reflective of central lung infarction surrounded by dense peripheral hemorrhage (**Fig. 5**).

Non-culture-based serologic tests for the diagnosis of invasive fungal infections are currently available. However, such serum markers, including 1,3-beta-D-glucan (BDG) and *Aspergillus* galactomannan, are derived from fungal cell wall components not

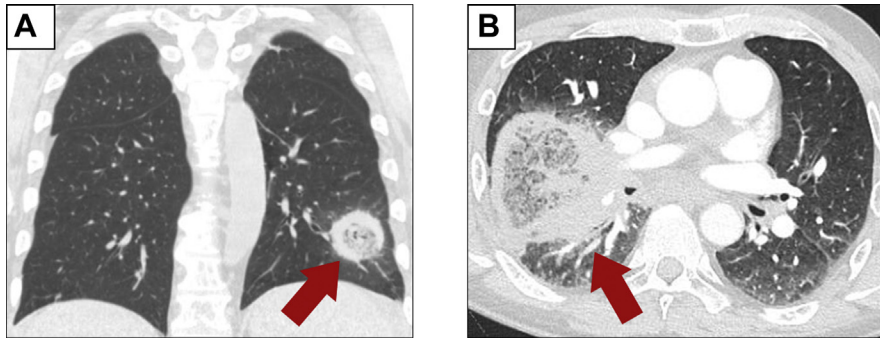


Fig. 5. Reverse halo sign (*arrows*) in patients with pulmonary mucormycosis (*A* and *B*).

present in Mucorales.[65,66] Thus, although a positive BDG or galactomannan can be suggestive of fungal infection with alternative pathogens to mucormycosis (ie, to "rule out" mucormycosis), these tests will not be able to identify a specific pathogen. Currently, there are no serum assays specific to mucormycosis.

Matrix-assisted laser desorption ionization-time of flight mass spectrometry can be used for better identification of culture specimens, but further development of available databases is necessary for more widespread use.[67] Molecular methods, including polymerase chain reaction–based approaches, are increasingly used because of their ability to improve detection in tissues, and often aid in identification to the level of the species, through targets such as the internal transcribed spacer or 18s ribosomal RNA.[60,67–71] Additional noninvasive approaches of fungal identification continue to be investigated as well, including gene expression profiling, next-generation sequencing, and breath-based metabolomics.[72–74]

MANAGEMENT

Early clinical recognition and prompt diagnosis are key in the management of mucormycosis. Although the clinical presentation and radiological features may be suggestive, urgent tissue diagnosis (pathology and culture) should be pursued whenever possible. Early initiation of systemic antifungals has a direct impact on the outcomes for mucormycosis and does not appear to alter the yield of tissue diagnosis or cultures.[75] Eliminating the predisposing factor should also be attempted, for example, achieving control of blood sugar in diabetes has shown to be an important component of treatment.[46] When eradication of the predisposing factor is not possible, such as in patients with hematological malignancies or transplant recipients, immunosuppression should be decreased as much as possible. Persistent immunosuppression (eg, persistent neutropenia) makes management of this infection extremely challenging (**Fig. 6**).

Amphotericin B (AmB) is the most active drug in vitro against Mucorales and is considered the drug of choice for initial therapy (**Table 1**).[76–79] For decades, AmB deoxycholate (AmB-D) was the sole available agent available for the treatment of mucormycosis. However, the use of AmB-D was limited by toxicity, especially

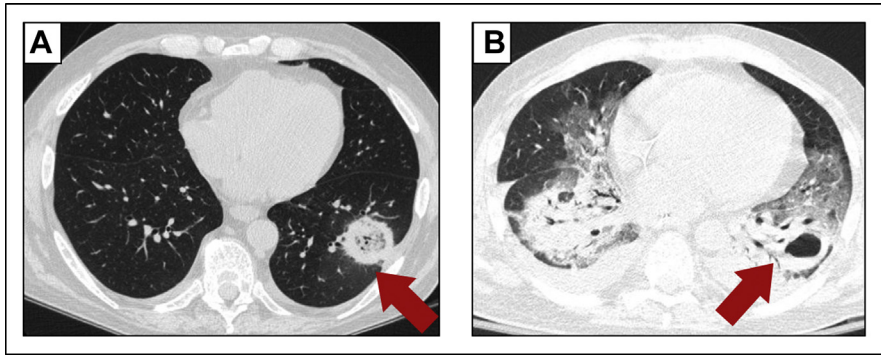


Fig. 6. (*A*) Chest CT scan demonstrates a masslike lesion in the left lower lobe, with a focal area of ground glass attenuation surrounded by a ring of consolidation (reverse halo sign [*arrow*]). (*B*) Repeat chest CT scan shows interval worsening of diffuse ground glass opacities bilaterally as well as cavitation (*arrow*) of previously noted masslike consolidation in the left lower lobe despite treatment with L-AmB in a patient with progression of acute leukemia.

Table 1
Antifungal drugs used for the treatment of mucormycosis

Antifungal Drug	Dose and Route	Common Side Effects
Initial therapy		
AmB -deoxycholate[a]	1–1.5 mg/kg/d IV	Infusion reactions Phlebitis Acute kidney injury Hypokalemia and hypomagnesemia Anemia
Liposomal AmB	5–10 mg/kg/d IV	
ABLC	5–10 mg/kg/d IV	
Step-down or salvage therapy		
Posaconazole	*IV formulation*: 300 mg twice daily on day 1, followed by 300 mg daily *Oral suspension*: 200 mg four times daily, followed by 400 mg twice daily after stabilization of disease.[b] *Delayed-release tablets*: 300 mg twice daily on day 1, followed by 300 mg daily[c]	Nausea, vomiting, diarrhea, and headache QTc prolongation Hepatotoxicity
Isavuconazole	*IV formulation*: 372 mg every 8 h for 6 doses, followed by 372 mg once daily *Oral tablets*: 372 mg (2 capsules) every 8 h for 6 doses, followed by 372 mg (2 capsules) once daily	Nausea, vomiting, diarrhea, headache, and rash Edema, hypokalemia Hepatotoxicity Shortened QTc interval Infusion reactions

[a] Infusion reactions (ie,: fever, rigors, nausea, and vomiting) are most frequent with AmB deoxycholate.
[b] Posaconazole oral suspension is taken with a full meal, liquid nutritional supplement, or acidic carbonated beverage to improve gastric absorption.
[c] Delayed release tablet Posaconazole is taken regardless of food intake, H2- receptor antagonists or proton pump inhibitors.

infusion-related reactions and nephrotoxicity. Lipid formulations of AmB with an improved safety profile were developed to obviate these frequent side effects. The AmB lipid complex (ABLC) is composed of large ribbonlike complexes of phospholipids; amphotericin B colloidal dispersion (ABCD) contains disclike structures of cholesteryl sulfate, and liposomal AmB (L-AmB) encompasses AmB within spherical liposomes.[80] The efficacy of lipid formulations of AmB appears to be comparable and perhaps even superior to that of AmB-D.[3,5,81–84] Of the lipid formulations, L-AmB and ABLC are most frequently used; the role of ABCD is limited and will not be discussed further. The use of lipid formulation AmB allows for prolonged therapy and higher daily doses with less toxicity; however, the optimal daily dosage of lipid formulations of AmB for mucormycosis has not been established. The usual dose for mucormycosis is 5 mg/kg/d, but higher doses (7–10 mg/kg/d) are used in severe cases.[80] Data suggest that high-dose L-AmB (10 mg/kg/d) does not improve outcome and increases toxicity.[85]

Among the azole class of antifungals, posaconazole and isavuconazole are the most active agents against Mucorales and are used for stepdown therapy after response has been achieved with AmB. Posaconazole and isavuconazole are also used as salvage therapy in patients that cannot be treated with AmB.[86,87] Mucorales are intrinsically resistant to other azoles (fluconazole, itraconazole, and voriconazole), echinocandins, and flucytosine.[88–90]

Posaconazole is active against Mucorales and comes in multiple formulations.[91] Two studies using oral suspension posaconazole as salvage therapy in patients with invasive mucormycosis have been reported.[92,93] Greenberg and colleagues[92] reported on 24 patients enrolled in an open-label salvage trial. In this study, 19 patients had infection refractory to AmB therapy. A favorable outcome (partial or complete response) was reported in 79% of patients, who were followed for 8 to 1004 days (median, 182 days). The variable endpoint used to assess response to therapy makes these results difficult to interpret, rather than the standard 6-week or 12-week endpoint used more frequently in antifungal trials. The second study is a retrospective review of 91 patients with refractory mucormycosis (48 with hematologic malignancies, 37 were transplant recipients, and 30 with diabetes).[93] In this study, the 12-week success rate was 60%. Both trials used the oral suspension of posaconazole, which has problematic absorption and must be administered multiple times daily with fatty food or a nutritional supplement. Breakthrough mucormycosis has been reported in patients receiving oral suspension posaconazole prophylaxis.[94] The occurrence of breakthrough infections could be a consequence of resistance of some Mucorales species to posaconazole or could be related to the poor absorption of the oral suspension resulting in suboptimal serum levels. New formulations of posaconazole, a delayed-release tablet and an intravenous formulation, are now available.[95,96] Extended-release tablet posaconazole offers a more reliable absorption independent of gastric acidity with fewer drug-drug interactions and side effects.[95,97] However, clinical data suggest that subtherapeutic levels can still occur and are linked to obesity, diarrhea, and the use of proton pump inhibitors.[98–100] Thus, therapeutic drug monitoring (TDM) is recommended for both treatment and prophylaxis.[101] Serum trough levels are recommended within 5 to 7 days after the first dose. The suggested serum level is greater than 0.7 μg/mL for prophylaxis, but levels $\geq$2 μg/mL are preferred for treatment of mucormycosis.

Isavuconazole is a newer triazole agent that is active against Mucorales, including *Rhizomucor* spp, *Rhizopus* spp, and *Mucor* spp.[89,102,103] Isavuconazole was granted Food and Drug Administration approval for the treatment of mucormycosis based on the results of a phase 3, open-label, noncomparative, multicenter study of invasive fungal infections that included 37 patients with invasive mucormycosis.[104] Of the 37 patients, 32 (86%) had proven invasive mucormycosis, and 5 (14%) had probable invasive mucormycosis. In this study, 16 patients (43%) received isavuconazole as salvage therapy after failing or being intolerant of standard therapy, whereas 21 patients (57%) received only isavuconazole. The overall success at day 42 was 32%, and mortality was 38%. Mortality was highest among patients with refractory disease (46%). In a separate matched case-control study, the outcomes of 21 patients treated with isavuconazole were compared with 33 patients treated with AmB. In this study, mortality was 33% in those receiving isavuconazole and 41% in those receiving AmB.[102] In addition, case reports have noted success with isavuconazole as salvage therapy for disseminated and sino-orbital mucormycosis when other therapies failed.[105,106]

Available data support the use of isavuconazole as an alternative to posaconazole for stepdown therapy following initial therapy with L-AmB. However, some species are resistant, and breakthrough cases of mucormycosis have been described in patients receiving either agent.[88,89,102,107,108] Recent literature has shown that Mucorales species exhibit varying degrees of sensitivity to isavuconazole leading to clinical failure.[107,109] Therefore, species identification and MIC testing should be obtained before initiating therapy with this agent. The role of isavuconazole TDM is uncertain, and routine monitoring is not recommended.[110] The use of isavuconazole in clinical practice will better define its future role in the treatment of mucormycosis.

Combination antifungal therapy is typically used by many physicians in an attempt to maximize treatment of this devastating disease, especially in patients with profound immunosuppression that cannot be reverted. The combination of lipid formulation AmB with oral posaconazole is based on case reports demonstrating efficacy.[111–113] However, in the absence of a clinical trial, it is not clear that the outcomes of combined therapy are significantly improved over those noted with lipid formulation AmB alone. Despite a paucity of data, many experts support the use of combination therapy with L-AmB and posaconazole, given the potential clinical benefit and the lack of evidence for antagonism between the drugs.

Echinocandins have also been used in combination with AmB despite their lack of activity against Mucorales.[114–117] A mouse model of mucormycosis infected with *Rhizopus oryzae* showed a modest improvement in survival when treated with caspofungin and AmB.[114] The clinical experience using combination therapy with echinocandins and AmB is limited to small retrospective series and case reports.[116,117] Although echinocandins have a very low side-effect profile, it is not clear that combination therapy has superior antifungal activity compared with monotherapy with L-AmB.[115,116] In rare cases, an echinocandin has been successfully combined with posaconazole in patients with anaphylaxis to AmB.[118] Currently, there are not enough data to support the routine use of an echinocandin combined with another antifungal agent for the treatment of mucormycosis.

It should be noted that the duration of antifungal therapy for mucormycosis is unknown, but typically ranges from months to years depending on organ involvement and the persistence of underlying risk factors (eg, ongoing immunosuppression or persistent neutropenia). Sequential clinical and radiological assessments are necessary to determine response to antifungal therapy, and management of these patients is typically personalized to their unique clinical circumstances.[67]

ADJUNCTIVE MANAGEMENT

Surgical debridement is instrumental in the treatment of this disease and has been shown to improve survival.[1–5,119] Thus, aggressive debridement of all necrotic tissue should be carried out expeditiously (see **Fig. 4**). Surgery is especially important in rhino-orbital mucormycosis.[3,6,120] Frequently, repeated debridements are required to effectively remove all necrotic tissue to a clean and viable surgical margin, increasing the effectiveness of antifungal therapy.[121,122] Particular sites of infection that are more difficult to access, such as the lungs, throat, or genitals, make surgical resection more challenging. Similarly, surgical debridement may be precluded in patients with hematological malignancy or hematopoietic stem cell transplant owing to severe thrombocytopenia.

Strategies to augment the number and function of neutrophils using granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor have shown benefit in animal studies.[115,121] However, human clinical data are limited by small patient numbers.[3,123–125] The use of interferon-gamma (IFN-γ) has also been used as an immunologic booster in patients receiving antifungal therapy for mucormycosis.[123] Case reports using IFN-γ have shown anecdotal success; however, there is not enough experience to recommend its routine use.

Rhizopus and other Mucorales require iron as a growth factor and use siderophores to capture iron from the host. Experimental animal studies have shown that the iron chelator deferasirox does not act as a siderophore and denies iron to *Rhizopus*, inhibiting its growth.[115] In a mouse model of mucormycosis, deferasirox efficacy was equal to that of AmB.[126] A few case reports and a small open-label salvage study appeared

to show benefit of deferasirox added to AmB or posaconazole therapy.[127,128] However, a double-blind, randomized study of L-AmB with either deferasirox or placebo showed no survival advantage.[129] In fact, 90-day mortality was significantly higher in patients who received the iron chelator. Based on these data, the use of deferasirox is not recommended as an adjuvant in the treatment of mucormycosis.

Hyperbaric oxygen has been used for adjunctive therapy in mucormycosis for many years.[130–132] However, its antifungal mechanism has not yet been fully determined. It is possible that the increased partial pressure of oxygen leads to an increase of free oxygen radicals that exert a fungicidal effect, increasing neutrophil phagocytosis and killing, as well as improving, angiogenesis.[131] The use of a hyperbaric oxygen adjunct to surgical and antifungal therapy may have a role in diabetic patients with sinusitis or those with cutaneous mucormycosis.[130,132] However, overall there is not enough experience using hyperbaric oxygen therapy to recommend its routine use in the treatment of mucormycosis.

SUMMARY

Invasive mucormycosis is a rare but aggressive fungal infection with high morbidity and mortality, particularly in patients with underlying medical comorbidities or immunosuppression. Clinical and radiographical presentations can vary between patients based on the immune status of the host and mode of infection. However, it is important to keep a high level of suspicion of infection, as early diagnosis and rapid initiation of surgical and antifungal therapy are key to improve survival.

CLINICS CARE POINTS

- Mucormycosis should be suspected in an immunosuppressed patient with skin lesions unresponsive to typical antibacterial agents.
- If mucormycosis is suspected, a biopsy specimen should be obtained. However, it is important to not delay empiric antifungal therapy with amphotericin while awaiting full diagnosis confirmation.
- When obtaining a biopsy specimen, tissue should be sent for both pathology and fungal culture.
- If mucormycosis diagnosis is confirmed, surgical debridement is key for treatment success whenever possible.
- Total antifungal duration for mucormycosis is typically prolonged (months to years), until clinical resolution is achieved. Lifelong therapy is sometimes necessary.

DISCLOSURES

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