Breaking the Mold: A Review of Mucormycosis and Current Pharmacological Treatment Options

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Abstract

Objective: To review the current literature for the pathogenesis of mucormycosis, discuss diagnostic strategies, and evaluate the efficacy of polyenes, triazoles, and echinocandins as pharmacological treatment options. **Data Sources:** An electronic literature search was conducted in PubMed using the MESH terms *Rhizopus*, zygomycetes, zygomycosis, *Mucorales* and *mucormycosis*, with search terms *amphotericin B, micafungin, anidulafungin, caspofungin, extended infusion amphotericin B, liposomal amphotericin B, combination therapy, triazole, posaconazole, isavuconazole, diagnosis*, and *clinical manifestations*. **Study Selection and Data Extraction:** Studies written in the English language from January 1960 to March 2016 were considered for this review article. All search results were reviewed, and the relevance of each article was determined by the authors independently. **Data Synthesis:** Mucormycosis is a rare invasive fungal infection with an exceedingly high mortality and few therapeutic options. It has a distinct predilection for invasion of endothelial cells in the vascular system, which is likely important in dissemination of disease from a primary focus of infection. Six distinct clinical syndromes can occur in susceptible hosts, including rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, widely disseminated, and miscellaneous infection. **Conclusion:** Diagnosis of mucormycosis is typically difficult to make based on imaging studies, sputum culture, bronchoalveolar lavage culture, or needle aspirate. Surgical debridement prior to dissemination of infection improves clinical outcomes. Surgery combined with early, high-dose systemic antifungal therapy yields greater than a 1.5-fold increase in survival rates. The Mucorales are inherently resistant to most widely used antifungal agents. Amphotericin B is appropriate for empirical therapy, whereas posaconazole and isavuconazole are best reserved for de-escalation, refractory cases, or patients intolerant to amphotericin B.

Keywords
Mucorales, isavuconazole, posaconazole, amphotericin B

Introduction

Invasive fungal infections are relatively rare because the human immune system efficiently eliminates the large pathogens. However, with advances in modern medicine, more individuals are susceptible to invasive fungal infections resulting from either immunosuppressive disease or immunosuppressive therapy. Treatment of invasive fungal infections is complicated because the drug target sites of eukaryotic pathogens closely resemble those of the human host, which limits therapeutic options. Mucormycosis is a rare invasive fungal infection with exceedingly high mortality and few therapeutic options. The purpose of this review is to highlight the epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment of invasive mucormycosis.

Data Search

An electronic literature search was conducted in PubMed using the MESH terms *Rhizopus, zygomycetes, zygomycosis,*

Mucorales and *mucormycosis*, with search terms *amphotericin B, micafungin, anidulafungin, caspofungin, extended infusion amphotericin B, liposomal amphotericin B, combination therapy, triazole, posaconazole, isavuconazole, diagnosis*, and *clinical manifestations*. Studies written in the English language from January 1960 to March 2016 were considered for this review article. All search results were reviewed, and the relevance of each article was determined by the authors independently.

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Taxonomy and Epidemiology

Mucormycosis is a broadly inclusive term used for infections caused by fungi in the phylum Zygomycota. In fact, zygomycosis and mucormycosis have historically been used interchangeably; however, in this review, mucormycosis will be used exclusively. The varied names and taxa that fall under the term *mucormycosis* reflect the ongoing controversy regarding the taxonomy of these fungi. The Zygomycota are phylogenetically diverse, and the validity of this phylum has been questioned, with some support for eliminating it entirely.[1]

The most common etiological agents of mucormycosis in humans belong to 2 orders: Mucorales and Entomophthorales. Within the Mucorales, the 4 genera most closely associated with disease in humans are *Rhizopus, Mucor, Absidia*, and *Cunninghamella*. The Entomophthorales contain 2 genera, *Conidiobolus* and *Basidiobolus*, which have been linked to human infections. These latter 2 genera are genetically and clinically distinct from the Mucorales. Of all the agents of mucormycosis, the single most frequently identified pathogen is *Rhizopus oryzae*, which may cause up to 70% of all cases.[2] For the purposes of this review, only the Mucorales will be discussed further.

The agents of mucormycosis are distributed worldwide and are ubiquitous in the environment. Infection is the result of inhalation of sporangiospores or inoculation of wounds. Rare cases have been linked to contaminated wound dressing or needles.[3-5] Mucormycosis is a quintessential opportunistic infection and generally affects severely compromised persons. Those most at risk include patients with diabetes with frequent episodes of ketoacidosis, burn and trauma patients, patients requiring iron chelation therapy, and persons severely immunocompromised by malignancy or chemotherapy. The incidence of mucormycosis is unknown and probably underestimated because diagnosis is difficult, and most cases in which a diagnosis is proven histologically or microbiologically are underreported.

Pathophysiology

Observational and experimental evidence unequivocally point to phagocytes as the primary host defense against mucormycosis. Persons with a very low absolute number of phagocytes or impaired phagocyte function have the greatest risk for invasive mucormycosis. Normal immune cells such as mononuclear and polymorphonuclear phagocytes readily take up and kill hyphae and spores of the molds that cause mucormycosis.[6] Neutropenia induced by cytotoxic chemotherapy is a well-known risk factor for mucormycosis. Additionally, patients with diabetes with poorly controlled blood glucose have chronically defective neutrophil function, and the acidic pH and hyperglycemia of ketoacidosis can acutely impair neutrophil motility and killing of internalized bacteria and fungi.[7] To a lesser extent, high-dose glucocorticoids can also impair phagocytosis and intracellular killing of ingested Mucorales spores.

One of the most intriguing and well-studied virulence mechanisms of these fungi is their capacity to sequester iron from the host. Iron is an essential cofactor for a variety of enzymes in nearly every organism, from prokaryotes to complex multicellular vertebrates. Free iron is essentially nonexistent under physiological conditions in humans, so infecting organisms must maintain some mechanism(s) to acquire iron within the host. Among the agents of mucormycosis, *Rhizopus* has been frequently used as a model organism to study iron acquisition. *Rhizopus oryzae* grows poorly in serum unless exogenous iron is added. If serum is acidified to pH <7.3 *Rhizopus* can grow more rapidly, presumably because acidic pH dissociates iron-protein complexes and makes more free iron available for the fungal cells.[8]

Some iron chelators can be significantly inhibitory to *Rhizopus* growth; however, others may function as siderophores and actually deliver iron to fungal cells and promote growth. Patients receiving deferoxamine for iron overload related to hemodialysis have a significant risk for mucormycosis.[9] Deferoxamine is a siderophore produced naturally by a wide variety of bacteria and can also function as a xenosiderophore to deliver iron to *Rhizopus* growing in vitro. Deferoxamine has an extremely high affinity for iron and can extract iron from transferrin and ferritin. *Rhizopus* can exploit deferoxamine as an iron source by expressing an inducible receptor, which takes up deferoxamine-iron complexes and reduces ferric to ferrous iron during intracellular transport.[10] The provisional *Rhizopus* genome contains 13 potential siderophore permeases; so it is likely that this organism and others of the Mucorales have multiple mechanisms to acquire scarce but essential iron ions from an environment that does not easily give them up.

Human pathogens within Mucorales have additional putative virulence factors that have been linked to pathogenesis. Mucormycosis has a distinct predilection for invasion of endothelial cells of the vascular system, and this capability is likely important in dissemination of disease from a primary focus of infection. *Rhizopus oryzae* has been shown to bind to macromolecules of the extracellular matrix in culture.[11] A cell-surface protein designated GRP78 is upregulated during glucose starvation and potentially acts as a receptor for Mucorales species in humans and permits uptake by and damage to endothelial cells.[12] Other suggested virulence factors of the Mucorales include secreted proteases and a ketone reduction pathway.[13,14] Of particular interest, certain taxa within Mucorales appear to express increased virulence in animal models following exposure to voriconazole.[15] Future deployment of newer azole agents may need to extend these observations to ensure that newer antifungals do not paradoxically accelerate mucormycosis disease progression.

Clinical Manifestations of Mucormycosis

The majority of data on clinical characteristics of mucormycosis come from case series and small studies on specific patient populations, such as those in oncology centers.[16] Six distinct clinical syndromes caused by invasive mucormycosis can occur in susceptible hosts, including rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, widely disseminated, and miscellaneous infection (Table 1). No clinical history is specific for the diagnosis of invasive mucormycosis.[17] The hallmark of disease is tissue necrosis resulting from angioinvasion and subsequent thrombosis; black, necrotic eschars (Figure 1) are common in affected tissues.[18] In many cases, the disease progresses rapidly and may result in death unless underlying risk factors are corrected and appropriate antifungal therapy and surgical excision are initiated.

Diagnosis of Mucormycosis

The diagnosis of mucormycosis is typically difficult to make based on imaging studies, sputum culture, bronchoalveolar lavage culture, or needle aspirate. A high index of suspicion is required to begin the appropriate diagnostic workup and treatment. *Proven* invasive fungal infection requires that the fungus be detected by histological analysis or culture of a tissue specimen taken from a site of disease. *Probable* invasive fungal infection requires the presence of a host factor (ie, recent history of neutropenia, prolonged use of corticosteroids >3 weeks, treatment with other T cell immunosuppressants within the past 3 months, etc), a clinical criterion (ie, evidence of lower-respiratory-tract fungal disease on imaging studies, tracheobronchitis, sinonasal infection, central nervous system [CNS] infection, etc), and a mycological criterion by direct (cytology, direct microscopy, or culture) or indirect (detection of antigen or cell-wall constituents) testing methods. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered a *possible* invasive fungal infection.[19]

Conventional radiological techniques are not specific in the diagnosis of pulmonary mucormycosis (Figure 2).[20] In a case series of 32 patients with pulmonary mucormycosis, the most common radiographical manifestation was progressive, homogeneous, lobar, or multilobar consolidation without significant lobar predilection. Less commonly, lung nodules or masses were found. Cavitation was seen in approximately 40% of cases.[21] In contrast, the use of high-resolution computed tomography (CT) and magnetic resonance imaging can be useful for the diagnosis of rhino-orbital-cerebral, pulmonary, and disseminated disease (Figure 3).[20] In a study of 8 patients with pulmonary mucormycosis, nodules or mass-like or wedge-shaped consolidation, particularly in the posterior segments of the upper lobes of the lung, were found to suggest mucormycosis on CT chest images; endobronchial lesions were less common.[22] The halo sign, a ground glass opacity surrounding a pulmonary nodule (reflecting hemorrhagic infarction), was associated with 78% of nodules in this study. Interestingly, others have found that the reverse halo sign, a rim of consolidation surrounding a center of ground-glass opacity on CT, is a strong indicator of pulmonary mucormycosis when compared with other invasive pulmonary fungal infections.[23,24]

Direct microscopic examination of sputum, paranasal sinus secretions, or bronchoalveolar lavage fluid is frequently nondiagnostic, but isolation of Mucorales organisms from any of these specimens in a susceptible host with corresponding clinical manifestations should be considered suspicious for infection.[17] Growth in culture on nonselective and fungus-selective media is typically rapid (preferably incubated at 37°C), covering the entire plate in a few days.[25] Negative cultures have been correlated with aggressive processing of the specimens before plating; grinding of specimens should be avoided.[26] Mucorales organisms typically have broad, ribbon-like, irregularly shaped, nonseptate (or sparsely septate) hyphae (diameter 6-25 μm), with branches arising at 45° to 90°.[25] They do not contain galactomannan (GM) or a significant amount of 1,3-b-D-glucan (BDG) in their cell walls. Thus, neither the BDG nor the GM assays are helpful in diagnosing this infection.[27] Definitive diagnosis of mucormycosis requires histological demonstration of the organism in affected tissues.[17] Histopathological examination typically reveals a predominantly neutrophilic inflammatory response; prominent infarcts and angioinvasion are seen in invasive disease.[25] Neutropenic patients have more extensive angioinvasion than nonneutropenic patients.[28] Molecular tools have also recently been developed to identify mucormycosis directly from tissue samples; fresh tissue is preferred over paraffin-embedded tissue because formalin damages DNA.[28,29]

Pharmacological Treatment Options

Successful treatment of mucormycosis is dependent on timely diagnosis and reversal of predisposing factors. Surgical debridement prior to dissemination of infection to distal organs and tissues has been shown to improve clinical outcomes.[25] When combined with early, high-dose systemic antifungal therapy, studies have shown a greater than 1.5-fold increase in survival rates.[30,31] The choice of antifungal therapy, however, is limited. The Mucorales are inherently resistant to most widely used antifungal agents.[32,33] In addition, limited antifungal susceptibility data as well as scarcely available MIC testing further reduce empirical antifungal options.
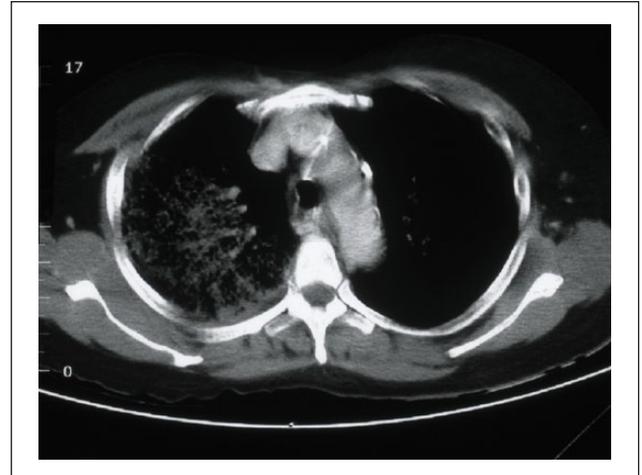
Table 1. Clinical Manifestations of Mucormycosis.

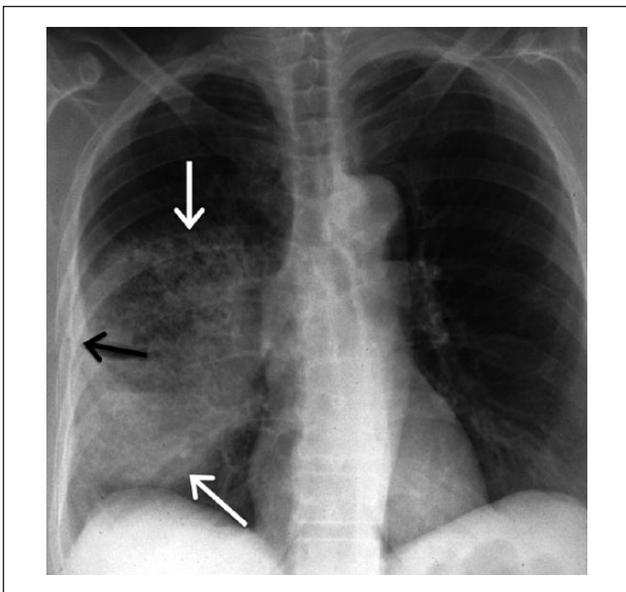|	Underlying Host Risk Factor	Pathogenesis of Disease State	Clinical Manifestations	Mortality Rate
Rhino-orbital-cerebral[16,66]	Diabetes mellitus, malignancy, HSCT, solid organ transplant	Begins in the paranasal sinuses after inhalation of sporangiospores, can spread to involve the palate, sphenoid sinus, cavernous sinus (leading to orbital involvement), and brain tissue	Sinusitis, periorbital cellulitis, eye/facial pain, facial numbness, blurry vision, orbital inflammation, proptosis, acute ocular motility changes, headache	50% Or higher depending on level of immunosuppression
Pulmonary[67-69]	Neutropenia, induction chemotherapy, HSCT with GVHD, lung transplantation	Hyphal invasion of pulmonary blood vessels, which can result in hemorrhage, thrombosis, ischemia, and infarction of distal tissue	Prolonged high-grade fever (>38°C), nonproductive cough, airway obstruction from endobronchial or tracheal lesions, massive hemoptysis if hilar blood vessels are invaded	66% Or higher depending on level of immunosuppression
Gastrointestinal[2,70,71]	Premature neonates, malnourished children, diabetes mellitus, immunosuppression	Ingestion of spore-contaminated fermented milk and porridges, dried bread products, alcoholic drinks derived from corn, herbal and homeopathic remedies; stomach most commonly affected followed by colon and ileum	Appendiceal, cecal, or ileac mass or gastric perforation; neutropenic patients may present with fever, typhlitis, and hematochezia	85%
Cutaneous[17,72]	Trauma/burn to the skin in a susceptible host	Caused by direct inoculation of fungal spores into the skin, may lead to disseminated disease; less likely to be caused by dissemination from internal organs to the skin	Varies from localized disease with gradual onset to progressive, fulminant disease, leading to gangrene and hematogenous dissemination; typically presents as necrotic eschar with surrounding erythema	Variable depending on disease severity; 25% in 1 case series
Disseminated[18,73]	Iron overload, profound immunosuppression, profound neutropenia, acute leukemia	Mucormycosis in 1 organ can spread hematogenously to another organ; lung is the site most commonly associated with dissemination	Varies widely, depending on the location of disease and degree of vascular invasion	Fatal without appropriate treatment
Miscellaneous[74]	Traumatic inoculation during surgical interventions, presence of contaminated medical devices (ie, catheters, adhesive tape, etc) in patients with underlying immunosuppressive disorders, contamination of food items	Contamination of medical equipment with fungal elements, foodstuffs contaminated with Mucorales such as barley, wheat, corn, oat, rice, onions, cotton, groundnuts, sweet potatoes, pecans, oranges, honey, and tomatoes	Skin infection, native or prosthetic valve endocarditis, osteomyelitis, peritonitis, pyelonephritis, gastrointestinal disease, and so on	Variable depending on location involved and degree of immunosuppression

Abbreviations: GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.
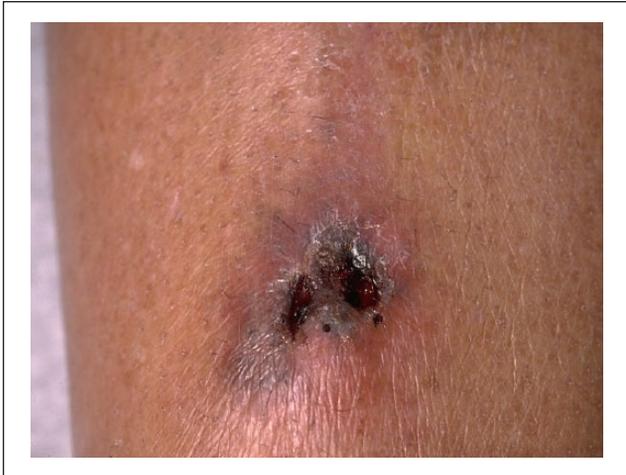
Figure 1. Necrotic eschar in a patient with cutaneous mucormycosis. Image appears with permission from VisualDx Logical Images, Inc.

Figure 2. Frontal chest radiograph of a patient with pulmonary mucormycosis demonstrating extensive consolidation in the right lung (white arrows). Regions of internal lucency are suggestive of cavitation. Adjacent pleural thickening and a small amount of pleural fluid are present (black arrow). Image appears with permission from VisualDx Logical Images, Inc.

Polyene Antifungals

Amphotericin B is largely considered the treatment of choice for mucormycosis. A polyene, amphotericin B exerts its antifungal activity by binding to sterols, preferentially ergosterol, which provides structure and rigidity to fungal cells. If the function of the cell membrane is limited, the fungal cell will leak, preventing the proliferation of the

Figure 3. Collimated, contrast-enhanced axial CT (computed tomography) image of a patient with pulmonary mucormycosis demonstrates airspace opacity and consolidation in the right lung. Image appears with permission from VisualDx Logical Images, Inc.

colony. If drug concentrations are high enough, the cell will die. For mucormycosis, the therapeutic dose of amphotericin B deoxycholate (ABD) is 1 to 1.5 mg/kg/d. A review of 170 cases of sinus mucormycosis showed that surgical debridement combined with ABD increased survival from 50% to 70%.[34] A review of 41 patients in case series with rhino-orbital-cerebral mucormycosis showed that only patients with both surgical debridement and ABD survived, albeit with a mortality rate of 52%.[35]

To reduce the incidence of nephrotoxicity in long-term therapy, many clinicians will choose a liposomal amphotericin B product (LAMB), and guidelines for mucormycosis published by the European Society for Clinical Microbiology and Infectious Diseases and the European Confederacy of Medical Mycology strongly favor LAMB 5 mg/kg over ABD.[25] The enhanced tolerability of LAMB allows the clinician to possibly push the dose beyond traditional limits and attempt to take advantage of potential fungicidal activity. In a murine model, LAMB and ABD did not differ significantly in survival rate in a lethal infection model of Mucorales, but LAMB outperformed ABD in some isolates when the LAMB dose was pushed to an equivalent dose of 10 mg/kg.[36] In pilot studies, such aggressive dosing also greatly enhanced nephrotoxicity to as high as 40% while providing no survival benefit.[37,38] Some practitioners use ABD in sequence with LAMB, only switching in the presence of adverse effects or failure. In a retrospective review of 120 mucormycosis cases, the mortality rate of sequential ABD/LAMB was 25% (n = 8) compared with LAMB alone, at 37.5% (n = 16), and both options outperformed ABD alone.[39] Of course, such retrospective evaluations of case series are subject to reporting bias and must be interpreted

with caution. Slowing the infusion rate of ABD up to a continuous infusion is another strategy to reduce nephrotoxicity, but it has not been studied in mucormycosis.

Triazoles

Triazoles, the largest class of antifungal agents in clinical use, exert their antifungal activity by inhibiting the 14-α demethylation of lanosterol in the ergosterol biosynthetic pathway. This leads to depletion and replacement of ergosterol with toxic 14-α-methylsterols, altering fungal membrane permeability as well as inhibiting membrane-bound enzymes involved in cell wall synthesis.[40] Of the second-generation triazoles, only posaconazole and isavuconazole display appreciable activity against the Mucorales. The addition of an α-*O*-methyl group to the chemical structure extends the spectrum of these drugs to include *Aspergillus* species and other filamentous fungi.[41,42]

Posaconazole

Posaconazole, which is structurally similar to itraconazole, has generally been considered second-line or salvage therapy for patients intolerant to amphotericin B.[40] One study evaluated 24 cases of mucormycosis in which patients received posaconazole as salvage therapy. All patients previously received some formulation of amphotericin B. Of these, 19 patients were considered refractory to previous therapy, whereas the other 5 patients were considered intolerant because of worsening renal function. The most common site of infection was rhino-orbital-cerebral. All patients received 800 mg/d of oral posaconazole suspension in divided doses. A complete response to therapy was seen in 11 of the 24 patients (46%), whereas partial response was seen in an additional 8 of 24 patients (23%). All 19 patients responding to posaconazole therapy survived.[43]

A retrospective study of 91 patients with either proven or probable mucormycosis also evaluated the effectiveness of posaconazole as salvage therapy. Greater than half of the study population received antifungal prophylaxis with triazoles prior to diagnosis. Patients received 800 mg/d of posaconazole suspension in divided doses for a minimum of 30 days. A 60% overall response rate was seen at 12 weeks postinitiation of posaconazole therapy.[44] Another retrospective evaluation of the effectiveness of posaconazole salvage therapy for invasive fungal infections found that in 4 cases of confirmed mucormycosis, there was a 50% survival rate.[45]

Until recently, posaconazole was only available as a suspension for oral administration. This dosage form provides a long-term option for patients with invasive fungal infections; however, the suspension displays variable pharmacokinetics. Case reports have shown that despite appropriate administration of the suspension, drug concentrations at the target site

are often significantly less than predicted.[46,47] Though age, gender, race, or ethnicity have no effect on its pharmacokinetics, commonly prescribed and coadministered medications significantly alter posaconazole bioavailability.[48] Elevations in gastric pH caused by coadministration with proton pump inhibitors reduce peak concentrations and the AUC (area under the curve) of posaconazole by 46% and 32%, respectively. Metoclopramide, , often used for its prokinetic/promotility properties, decreases gastrointestinal transit time, significantly reducing drug absorption.[49,50] Potent inducers of hepatic cytochrome P450 enzymes, such as phenytoin and rifampin, drastically increase posaconazole's clearance from the body. Also, commonly seen clinical complications of immunosuppression or chemotherapy, such as diarrhea and mucositis, negatively affect absorption.[50]

The introduction of the tablet formulation addresses most of the absorption concerns with oral posaconazole. The delayed-release tablet achieves more than twice the median serum posaconazole levels seen with the suspension.[51] The tablet should be given as 300 mg orally twice on day 1, followed by 300 mg orally once daily and can be taken without regard to food. The intravenous formulation provides an alternative for patients intolerant to the oral formulations and is dosed the same as the delayed-release tablet. The 300-mg intravenous dose achieves 2 to 4.5 times the peak serum concentration of single oral doses of 400 and 800 mg of the suspension, respectively.[52,53] The impact the delayed-release tablet and intravenous formulation will have on the treatment of mucormycosis is still unknown. In cases in which posaconazole therapy is appropriate, a once-daily regimen is ideal for long-term therapy. Once-daily infusions should be beneficial to patients with malabsorption or an inability to use the gastrointestinal tract.

Isavuconazole

Isavuconazole, an extended-spectrum triazole structurally similar to fluconazole, is the only azole antifungal approved for the treatment of invasive mucormycosis. Currently available as its prodrug, isavuconazonium sulfate, it is rapidly metabolized by serum butylcholinesterase to its active form. The approved dose of isavuconazonium sulfate for invasive mucormycosis is 372 mg (equivalent to 200 mg isavuconazole) given every 8 hours for 6 doses, followed by 372 mg daily.[54] In vitro, isavuconazole has displayed activity, though variable, to *Lichtheimia, Rhizopus, Mucor*, and *Cunninghamella* spp. Wide minimum inhibitory concentration (MIC) ranges for isavuconazole exist throughout these genera, with the lower end of reported MIC ranges being similar to those reported with posaconazole.[55]

To date, there are 2 published case reports displaying the use of isavuconazole as salvage therapy for invasive mucormycosis. The first involved a 59-year-old man with

myelodysplastic syndrome status post–hematopoietic stem cell transplantation. Three weeks later the patient was found to have pulmonary mucormycosis caused by *Rhizomucor pusillus/Rhizopus miehei*. The patient was given LAMB at 5 mg/kg once daily for 4 weeks, with some improvement noted. On discharge, the patient was switched to oral posaconazole suspension 800 mg in divided doses daily but was subsequently readmitted with new-onset seizures and altered mental status. CT of the head showed multiple brain lesions, with associated surrounding edema. LAMB was reinitiated; however, the patient developed significant nephrotoxicity. Authorization was obtained to treat the patient with oral isavuconazole at the approved dosage. At 19 weeks into isavuconazole treatment, chest CT showed significant improvement, and head CT showed decreased size of the brain lesions with no surrounding edema.[47]

The second patient was a 45-year-old man with rhino-orbital-cerebral mucormycosis, likely caused by previous use of high-dose oral steroids. The isolate identified was *Rhizopus oryzae* species. MICs were reported as 0.5 mg/L for amphotericin B, 3 mg/L for posaconazole, and 1 mg/L for isavuconazole. Combination therapy with LAMB (5 mg/kg/d) and twice-daily posaconazole (800 mg/d) was started and administered for 92 and 52 days, respectively. Despite 24 days of posaconazole therapy, concentrations in the soft tissue remained below the MIC of the fungal isolate. Also, worsening of renal failure led to the use of intermittent hemodialysis. At day 61, tissue biopsies still revealed the presence of filamentous fungal elements. Therapy was discontinued, and the patient was started on isavuconazole at the approved dose on day 104 of hospitalization. By day 174, the patient was discharged and continued on once-daily isavuconazole. Monotherapy with isavuconazole continued for a total of 506 days. Follow-up biopsies obtained up to 1 year post–isavuconazole therapy gave negative results for filamentous fungal elements.[46]

Only 1 trial has prospectively studied the effectiveness of a triazole antifungal agent as initial treatment of invasive mucormycosis. An open-label noncomparative trial evaluated the safety and efficacy of isavuconazole in 37 patients with probable or proven mucormycosis. The most common pathogens identified were *Rhizopus oryzae* and *Mucormycetes*. In all, 59% of patients had pulmonary involvement, though half of these had disseminated infection. The most common nonpulmonary locations involved were the sinus (43%), orbit (19%), CNS (16%), and bone (14%). Patients receiving isavuconazole were classified as primary therapy, invasive mold disease refractory to other antifungal therapy, or patients intolerant to other antifungal therapy. All study participants received 200 mg orally or intravenously every 8 hours for 6 doses, followed by 200 mg once daily for a median duration of 102 days (primary), 33 days (refractory), and 85 days (intolerant), respectively. All-cause mortality through day 42 was 38% between groups

(33% primary, 45% refractory, 40% intolerant). The overall response success rate at end of treatment, however, was 31% between groups. Though this study neither compared isavuconazole with other available options, nor randomized participants, it does provide clinical evidence for the effectiveness of isavuconazole in treating mucormycosis.[54]

Echinocandins and Combination Therapy

Although echinocandins have no inherent activity against mucormycosis, there is some early evidence that they may augment polyene therapy. The mechanism of action differs from that of the polyenes by inhibiting cell wall component β-1, 3-glucan. This activity in filamentous fungi is largely fungistatic. In vitro and murine models suggest that echinocandins may be added to a polyene backbone for enhanced therapeutic success, particularly in *Rhizopus* spp. and rhino-orbital-cerebral mucormycosis.[56,57] The mechanism of action may be related to some species expressing the target component for echinocandins. In 1 study over a 12-year period, 41 patients with mucormycosis were evaluated for treatment success at 30 days. Six of the patients were on both a polyene and an echinocandin (caspofungin). The success rate in patients with combination therapy was significantly higher than that in those who received amphotericin B monotherapy.[58] In contrast, a study comparing eras before and after combination therapy (n = 101) showed no difference in 90-day mortality between the 2 groups despite a 6-fold increase in the use of combination therapy.[59]

For patients unable to tolerate amphotericin B, a combination of caspofungin and posaconazole was successful in 2 patients, with potential synergistic effects between the 2 medications.[60] In a case report, a patient with rhino-orbital-cerebral mucormycosis failed amphotericin B monotherapy and was successfully treated with a combination of high-dose LAMB and caspofungin followed by long-term posaconazole, hyperbaric oxygen, and strict diabetic control.[61] Such combination therapies are exciting, but the supporting evidence is not robust enough to recommend them as first-line therapy in all cases. A recent study retrospectively evaluated 106 mucormycosis patients treated initially with either combination or monotherapy. Mortality was 41% and 43% in the combination and monotherapy groups, respectively.[62] In addition, there are significant questions as to which organisms or infections will respond to combination therapy at all. Also, the correct dose of echinocandins is not well described. However, combination therapy with echinocandins maintains a niche as salvage therapy in mucormycosis.

Summary

Though timely initiation of antifungal therapy for mucormycosis is certainly an important variable as it relates to

efficacy of treatment, the viable choices of antifungal agents are less than ideal. Agents used as initial empirical therapy should possess appreciable activity against the most likely causative pathogen(s) and have low rates of resistance, flexible routes of administration, few adverse events, and limited drug-drug interactions.[63]

Of the agents discussed, amphotericin B possesses the largest spectrum of antifungal activity and susceptibility. An in vitro study of more than 200 clinical isolates found that for the Mucorales as a whole, amphotericin B displayed the most antifungal activity, with the majority of isolates displaying MICs of ≤1 mg/L.[32] Another in vitro study found AMB to be the most effective agent against Mucorales; however, MICs of 2 mg/L were found in 3/19 *Rhizopus* strains and 5/8 *Cunninghamella* strains tested.[64] Despite the preferential use of liposomal formulations, long-term tolerability to AMB remains a concern. In addition, patients receiving AMB require a central venous catheter, which, depending on the duration of therapy, may increase the likelihood of blood stream infections to already at-risk patients.

Of the triazoles, posaconazole appears to be the most effective agent in vitro to the Mucorales. One in vitro study found that all strains tested were inhibited by concentrations of 2 mg/L. However, *Mucor* spp. and *Cunninghamella* spp. show significantly lower degrees of susceptibility in this study.[64] Even so, failures to posaconazole therapy still exist irrespective of genera because of poor drug concentrations at the infection site.[46,47] Also, bioavailability of the oral suspension is significantly reduced because of some drug-drug interactions and food-drug interactions. Though newer delayed-release tablets and intravenous formulations are now available, how this affects posaconazole's use in mucormycosis is yet to be seen.

Isavuconazole presents a unique conundrum in the battle against mucormycosis. When studied in vitro, isavuconazole displayed limited or partial antifungal activity against Mucorales. In fact, less than 28% of *Rhizopus* spp. showed a MIC of <2 mg/L.[65] Despite this, however, patients treated with isavuconazole as primary therapy had a 33% mortality rate in the open-label study.[54] Specifics about individual patients in this study group are currently unavailable. In addition, MIC breakpoints for resistance have yet to be established. In the 2 published case reports, initial serum and target site concentrations of isavuconazole were less than predicted, leading to short-term dose increases. Although this could certainly be a result of a lack of familiarity with the drug, it further highlights the difficulty in treating invasive mold diseases in poorly perfused infectious sites. Also, though no human data currently exist, there remains concern related to triazoles paradoxically accelerating mucormycosis disease progression.[15]

Conclusion

Based on the available evidence, amphotericin B is the appropriate empirical antifungal for invasive mucormycosis. Utilizing the liposomal formulations or other strategies to reduce nephrotoxicity is prudent. De-escalation to posaconazole or isavuconazole remains a viable strategy once the pathogen and susceptibility to these agents are identified. In addition, the availability of oral formulations for these agents makes them desirable choices for long-term treatment. In cases of amphotericin treatment failure or intolerability, these triazoles may serve as effective salvage options. The caveat, however, is that treatment durations typically exceed 1 or 2 years.[43,46,47] Thus, patient tolerability and interactions related to drugs, food, and concomitant disease states should be closely monitored.

Pharmacists play an important role in the treatment of mucormycosis. Monitoring patients for adverse events related to drug administration as well as alterations in the pharmacokinetics and pharmacodynamics of each medication resulting from interactions and underlying medical conditions is prudent to the care of these patients.

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