

# Mucormycosis is the Deadly Fungal Infection

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## ABSTRACT

*Mucormycosis (previously called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These molds live throughout the environment. Mucormycosis mainly affects people who have health problems or take medicines that lower the body's ability to fight germs and sickness. It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury. Rhino-orbital-cerebral presentation associated with uncontrolled diabetes is the predominant characteristic. Isolated renal Mucormycosis has emerged as a new clinical entity. Apophysomyces elegans and Rhizopus homothallicus are emerging species in this region and uncommon agents such as Mucor irregularis and Thamnostylum lucknowense are also being reported.*

*It is generally spread by breathing in, eating food contaminated by, or getting spores of molds of the Mucorales type in an open wound. These fungi are frequently present in decomposing organic matter such as rotting fruit and vegetables, leaves, and animal manure, but do not usually affect people. It is not transmitted between people. Risk factors include diabetes, lymphoma, organ transplant, iron overload, HIV/AIDS and long-term steroids or immunosuppressant's.*

**Key words:** HIV/AIDS, lymphoma, Mucormycosis, Mucorales

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## INTRODUCTION

Mucormycosis (previously called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These molds live throughout the environment. Mucormycosis mainly affects people who have health problems or take medicines that lower the body's ability to fight germs and sickness. It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury [1].

Based on anatomic localization, Mucormycosis can be classified as one of 6 forms rhino cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and uncommon presentations.

Rhino-orbital-cerebral presentation associated with uncontrolled diabetes is the predominant characteristic. Isolated renal Mucormycosis has emerged as a new clinical entity. Apophysomyces elegans and Rhizopus homothallicus are emerging species in this region and uncommon agents such as Mucor irregularis and thamnostylum lucknowense are also being reported.

It is generally spread by breathing in, eating food contaminated by, or getting spores of molds of the Mucorales type in an open wound [2,3]. These fungi are

frequently present in decomposing organic matter such as rotting fruit and vegetables, leaves, and animal manure, but do not usually affect people. It is not transmitted between people. Risk factors include diabetes, lymphoma, organ transplant, iron overload, HIV/AIDS and long-term steroids or immunosuppressant's.

## MATERIAL AND METHODS

### PATHOGENESIS

*Rhizopus* organisms have an enzyme, ketone reductase, which allows them to thrive in high glucose, acidic conditions. Serum from healthy individuals inhibits growth of *Rhizopus*, whereas serum from individuals in diabetic ketoacidosis stimulates growth.

Rhino-orbital-cerebral and pulmonary mucormycosis are acquired by the inhalation of spores. In healthy individuals, cilia transport these spores to the pharynx and they are cleared through the gastrointestinal tract. In susceptible individuals, infection usually begins in the nasal turbinate's or the alveoli the agents of mucormycosis are angioinvasive; thus, infarction of infected tissues is a hallmark of invasive disease [4].

### Deferoxamine and iron overload

Deferoxamine, which chelates both iron and aluminium, increases the risk of mucormycosis by enhancing growth and pathogenicity. The deferoxamine-iron chelate, called feroxamine is a siderophore for the species *Rhizopus*,

increasing iron uptake by the fungus, which stimulates fungal growth and leads to tissue invasion.

Iron overload itself may predispose to mucormycosis in the absence of deferoxamine therapy. In addition, individuals with diabetic ketoacidosis have elevated concentrations of free iron in their serum, which supports the growth of *Rhizopus oryzae* at an acidic, but not at an alkaline, pH.

Deferoxamine was once used commonly as an aluminium chelator in patients with renal failure however, aluminium excess is rarely seen today. Currently, patients at risk for deferoxamine-associated mucormycosis are those who have received multiple blood transfusions and are treated with this chelating agent for iron overload [5,6]. The majority of patients with deferoxamine-associated infection present with disseminated disease that is rapidly fatal, with a mortality rate that approaches 90 percent.

### DIAGNOSIS

The diagnosis of mucormycosis relies upon the identification of organisms in tissue by histopathology with culture confirmation. However, culture often yields no growth, and histopathology identification of an organism with a structure typical of Mucorales may provide the only evidence of infection.

A clinician must think of this entity in the appropriate clinical setting and pursue invasive testing in order to establish a diagnosis as early as possible. On the other hand, the agents of mucormycosis can colonize the airways or be contaminants in cultures, and the isolation of these fungi in a culture does not necessarily prove infection. Interpreting the culture results in the context of the patient's signs and symptoms and underlying disease are necessary to determine whether antifungal therapy should be given.

Serum tests, such as the 1,3-beta-D-glucan assay and the Aspergillium galactomannan assay, are being used with increased frequency in patients suspected of having an invasive fungal infection. The agents of mucormycosis do not share these cell wall components and neither test is positive in patients with mucormycosis.

Investigational studies have demonstrated the feasibility of using polymerase chain reaction (PCR)-based techniques on histological specimens. In one study of patients with proven mucormycosis, among 12 cases that were positive by culture, 10 were also positive by PCR, and sequencing was concordant with culture results to the genus level in 9. Among 15 culture-negative cases, PCR was positive and sequencing allowed genus identification in 12. The PCR-based technique used in this study appears promising for establishing the diagnosis of mucormycosis when cultures are negative.

In addition to traditional culture techniques and PCR with sequencing, matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry can be used to identify the causative species from culture specimens.

### Rhino-orbital-cerebral infection

The presence of mucormycosis should be suspected in high-risk patients, especially those who have diabetes and metabolic acidosis and who present with sinusitis, altered mentation, and/or infarcted tissue in the nose or palate.

Endoscopic evaluation of the sinuses should be performed to look for tissue necrosis and to obtain specimens. The specimens should be inspected for characteristic broad, nonseptate hyphae with right-angle branching using calcofluor white and methylamine silver stains. The presence of the characteristic hyphae in a clinical specimen provides a presumptive diagnosis that should prompt further evaluation. However, the absence of hyphae should not dissuade clinicians from the diagnosis of mucormycosis when the clinical picture is highly suggestive.

Further evaluation includes imaging to gauge sinus involvement and to evaluate contiguous structures such as the eyes and brain. We generally perform a computed tomography (CT) scan as the initial imaging study as it can often be obtained quickly and is more sensitive than magnetic resonance imaging (MRI) for detecting bony erosions. Clinicians should have a low threshold for performing an MRI in patients with abnormalities on CT because the MRI will enhance detection of intracranial, intraorbital, and cavernous sinus involvement. In a study of 23 immunocompromised patients with fungal sinusitis, CT findings included severe soft tissue edema of the nasal cavity mucosa in 21 patients, sinus mucoperiosteal thickening in 21 patients, bone erosion in 8 patients, orbital invasion in 6 patients, facial soft tissue swelling in 5 patients, and retroantral fat pad thickening in 2 patients.

### Pulmonary infection

The diagnosis of pulmonary mucormycosis is difficult because the presentation does not differ from pneumonia due to other angioinvasive molds. Isolating an agent of mucormycosis from respiratory cultures in a high-risk patient with a compatible clinical presentation is an indication for starting empiric treatment. Establishing a definitive diagnosis can be difficult because it requires demonstration of the organism in tissue. Because obtaining tissue can be difficult in these cases, we often rely on radiographic evidence to support the diagnosis.

Chest radiographs or CT scans may demonstrate focal consolidation, masses, pleural effusions, or multiple nodules. A halo sign (ground-glass attenuation surrounding a nodule) is characteristic of angioinvasive fungi, but a reversed halo sign, a focal area of ground-glass attenuation surrounded by a ring of consolidation, has also been reported. Mucormycosis appears to be the most common condition to cause the reversed halo sign in immunocompromised hosts. In a retrospective study that included 189 patients with proven or probable fungal pneumonia, the reversed halo sign was seen in 7 of 37 patients with mucormycosis 1 of 132 patients with invasive aspergillosis.

Radiographic evidence of infarction with cavitary lesions and an air crescent sign is unusual. In a series of 45 cases, the following features were independent predictors of mucormycosis and helped to differentiate it from aspergillosis: concomitant sinusitis, >10 pulmonary nodules on CT scan, pleural effusion, and prior voriconazole prophylaxis.

Sputum or bronchoalveolar lavage (BAL) specimens can show the characteristic broad nonseptate hyphae, which is often the first indicator of mucormycosis. However, in one case series, only 25 percent of sputum or BAL specimens were positive pre-mortem. Hyphae can also be demonstrated on lung biopsy.

### Other syndromes

The diagnosis of gastrointestinal mucormycosis can be made with endoscopic biopsy of the lesions that show the characteristic hyphae. For isolated renal involvement, percutaneous biopsy or nephrectomy can establish a diagnosis. Urine cultures are almost always sterile. Imaging of the kidneys with CT can demonstrate either ill-defined areas of low attenuation and diminished enhancement suggestive of pyelonephritis or multiple small foci suggestive of abscesses.

In isolated central nervous system involvement, CT scan usually shows poorly enhancing lesions; cerebrospinal fluid cultures are negative. Diagnosis can be made with biopsy or resection of the involve.

### Microscopic examination and culture

Microscopy and culture of various clinical specimens are the cornerstones of diagnosing mucormycosis.

Direct microscopy of clinical specimens, preferably using optical brighteners such as Blankophor and Calcofluor White in clinical specimens allows a rapid presumptive diagnosis of mucormycosis. Hyphae of Mucorales have a variable are nonseptate or pauci-septate and show an irregular, ribbon-like appearance. The angle of branching is variable and includes wide-angle bifurcations. Fungal elements may easily be seen on haematoxylin and eosin sections; Periodic acid-Schiff or Grocott-Gomori's methylamine silver staining are used to highlight fungal hyphae and hence to evaluate morphology in more detail. Tissue histopathology is dominated by inflammation which may be neutrophilic or granulomatous; inflammation seems to be absent in a few cases, particularly in immunosuppressed patients. Invasive disease is characterized by prominent infarcts and angioinvasion. In cases where nerve structures are involved a perineural invasion may be present. Neutropenic patients display a more extensive angioinvasion when compared to nonneutropenic patients. Histopathological examination of tissue specimens may not always allow a reliable differentiation between hyphae of *Aspergillus* or morphologically related fungi, and hyphae of Mucorales. However, tissue identification is a very important diagnostic tool, since it distinguishes the presence of the fungus as a pathogen in the specimen from a culture contaminant. All Mucorales

grow rapidly on most fungal culture media, such as Sabouraud agar and potato dextrose agar incubated at 25°C to 30°C. For some species, a microaerophilic environment improves culture yield. Paradoxically, even when fungal hyphae are seen in histopathologic analysis, fungal cultures are only positive in 50% of cases. Hyphae are friable in nature and hence may be damaged during tissue manipulation.

A specific mouse monoclonal anti-Rhizomucor-antibody has been employed for immunohistochemical analysis; however, this test was previously shown to react with other Mucorales and Entomophthorales. The use of in situ hybridization targeting 5S and 18S ribosomal RNA sequences remains investigational.

### Species identification and antifungal susceptibility testing

Species identification is of interest for a better epidemiological understanding of mucormycosis and may be of value for outbreak investigations.

Mucorales fungi can easily be differentiated from *Aspergillus* fungi on culture. The study by Alvarez demonstrated that morphological features alone, when assessed by individuals with expertise in fungal identification, can provide a high level of accuracy. However, morphological species identification is difficult and may be associated with failures in speciation. ID32C kit has been used successfully for the identification of *Lichtheimia corymbifera* and *R. pusillus* and API 50CH (bioMérieux) for *Mucor* species. *M. circinelloides* and *M. rouxii* failed to be distinguished by either test. ID32C combined with positive melezitose assimilation detects *L. ramosa*. Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry is a promising tool, but is not yet validated for all Mucorales. Another reliable approach is the application of molecular based assays focusing on the internal transcribed spacer region.

*M. circinelloides* shows high minimum inhibitory concentrations (MIC) against posaconazole, and *Rhizopus* and *Cunninghamella* against amphotericin B. Some *Apophysomyces* isolates have also increased MIC against amphotericin B. The role of such data is unclear for patient treatment but needs to be further analyzed.

None of the controls had Mucorales-specific T cells. The use of such specific T cells as surrogate diagnostic markers will be the subject of further studies.

### Molecular assays

Molecular based assays include conventional polymerase chain reaction (PCR) restriction detection or identification of Mucorales. The majority of the molecular assays target either the internal transcribed spacer or the 18S rRNA genes. 39,41 Several studies have been done using either formalin-fixed, paraffin-embedded or fresh tissue samples<sup>3</sup> yet resulting in different performance. Sensitivity and specificity varied among the studies performed, with the greatest disadvantage being the low

number of patients studied. The efficiency of these in-house assays has not been widely studied, lacks thoroughly clinical evaluation and therefore can't be recommended as stand-alone, single approach in clinical routine diagnostics. Recent attempts directed at molecular-based diagnosis from blood and serums have yielded promising clinical data. Molecular-based diagnosis from serum resulted in earlier diagnosis when compared to culture, and overall confirmed culture-proven cases. Presently, molecular-based diagnostic assays can be recommended as valuable add on tools that complement conventional diagnostic.

### Treatment

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

Available data indicate advantages of LAmB over amphotericin B lipid complex for the treatment of CNS mucormycosis. For example, LAmB levels achieved in rabbit brain were fivefold above ABLC levels. Furthermore, while similarly effective in neutropenic mice, LAmB was markedly superior to ABLC in diabetic ketoacidotic mice infected with *Rhizopus oryzae*, primarily because of superior clearance of fungus from the brain. These animal studies are complemented by a recent, relatively small retrospective case series, in which the outcomes of patients with rhino-orbital-cerebral mucormycosis were found to be worse when ABLC was used as initial therapy versus AmB or LAmB.

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

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

result in pharmacokinetic advantage compared to 10 mg/kg/d.

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

In contrast, reported 60% response rates for salvage therapy in patients with mucormycosis who were refractory to or intolerant of polyenes. Reported similar results. Hence, posaconazole is an option for salvage therapy for these infections.

### Combination Antifungal Therapy for Mucormycosis

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

In a recent retrospective review from two institutions, combination polyene-caspofungin therapy was associated with significantly improved outcomes in patients with rhino-orbital and rhino-orbital-cerebral mucormycosis compared to polyene monotherapy. Most of the patients were diabetic, although some patients in the series had neutropenia or were solid-organ transplant recipients. In multivariate analysis, only combination therapy was significantly associated with superior outcomes.

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

if combination lipid polyene-echinocandin therapy is superior to monotherapy.

The central role of iron in pathogenesis of mucormycosis has been confirmed based on and animal models, and retrospective human studies. The requirement for iron acquisition for *R. oryzae* growth and pathogenesis suggested that abrogation of iron uptake could be an important therapeutic adjunct for mucormycosis infections. Indeed, the iron chelators deferasiprone and deferasirox, the latter of which is approved by the US Food and Drug Administration to treat iron overload in transfusion-dependent anemias improved survival in rodents with mucormycosis. Deferasirox was cidal for 28 of 29 clinical isolates *Mucormycotina* with an MIC<sub>90</sub> of 6.25 µg/mL. The drug exhibited time-dependent killing, with cidality occurring at 12–24 h of drug exposure. Based on trough serum levels of greater than 15 µg/mL in patients treated with deferasirox at 20 mg/kg/d, it should be feasible to maintain serum levels in excess of the MICs of *Mucormycotina* throughout the entire dosing interval.

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

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

No clinical data exist to address the role of combination posaconazole-polyene therapy for mucormycosis. However, two recent pre-clinical studies evaluated the efficacy of posaconazole combination therapy during murine mucormycosis. In the first study. Found that

combining posaconazole with AmB enhanced the survival of neutropenic mice infected with *R. oryzae* only when compared to a subtherapeutic dose of AmB monotherapy (0.3 mg/kg/d). In contrast, combination therapy was of no advantage compared to AmB monotherapy at a standard dose. Similarly, we recently reported that combination posaconazole plus LAmB was of no benefit compared to monotherapy with LAmB alone in either neutropenic or DKA mice with mucormycosis. Based on available data, posaconazole does not have a clear role as adjunctive therapy in combination with lipid polyenes.

Ben-Ami recently reported that the antibacterial agent, colistin, has activity against the *Mucorales*. Colistin was cidal although regrowth of the fungus occurred unless subinhibitory AmB was added for synergy. Colistin's mechanism of action appeared to involve disruption of the cytoplasmic and intracellular vacuolar membrane integrity. The drug had limited activity as a prophylactic agent during inhalational challenge, but did not have systemic therapeutic activity. Its potential role as a second agent in a combination regimen merits further study.

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

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

### SALVAGE THERAPY

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

Experience is limited with deferasirox as salvage therapy. However, in case series and case reports, its addition to patients progressing on previous therapy has resulted in favourable outcomes without substantive toxicity. If deferasirox is used, it should be used cautiously and with regular monitoring of renal and hepatic function. Administration at a dose of 20 mg/kg/d for 2–4 weeks is

reasonable for salvage therapy, because in pre-clinical studies of non-iron-overloaded primates, deferasirox toxicity increased beyond 4 weeks of therapy.

G-CSF-mobilized granulocyte transfusions may provide additional support for persistently Neutropenic patients until recovery from Neutropenic.

#### CONCLUSION

Administration of GM-CSF or IFN- $\gamma$  may further augment host response and antifungal effect in non-neutropenic patients with refractory infection. In a recent murine study, addition to LAmB therapy of GM-CSF, but not IFN- $\gamma$ , improved the survival of mice with mucormycosis.

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