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# Agents of Mucormycosis and Entomophthoramycosis

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# Abstract

Mucormycosis is an aggressive fungal infection, caused by filamentous fungi in the subphylum Mucoromycotina, order Mucorales, that primarily afflicts patients undergoing treatment for hematologic malignancies, hematopoietic or solid-organ transplantation, and patients with severe hyperglycemia and/or ketoacidosis. In immunocompetent patients Mucorales can cause necrotizing skin and soft tissue infections after penetrating trauma or burns, or, less frequently, nosocomial outbreaks of infection after contamination of bandages and bed linens. The most common forms of mucormycosis are rhinocerebral disease and sinopulmonary, cutaneous, gastrointestinal (GI), and disseminated infections. A high index of suspicion is essential for early diagnosis of mucormycosis because early clinical and radiographic signs are nonspecific. The development of severe sinusitis, orbital swelling, necrotic lesions of the turbinates or hard palate, and nodular infiltrates, on occasion with a reverse halo sign, are highly suggestive signs of infection, especially among immunocompromised patients receiving voriconazole or echinocandins. Diagnosis is typically established by histopathologic documentation of “ribbon-like” angioinvasive hyphae in tissue, although molecular and immunologic-based diagnostics have been investigated. Lipid formulations of amphotericin B remain the drugs of choice. Oral posaconazole, or possibly isavuconazole, is used for treatment once infection is clinically stable. This chapter also discusses entomophthoramycosis, a rare infection of the paranasal sinuses, subcutaneous tissues, or GI tract caused by filamentous fungi of the order Entomophthorales, which was historically grouped with mucormycosis under the general term zygomycosis, which is now considered an obsolete term due to changes in taxonomy.

# Keywords

amphotericin B

antifungal

*Apophysomyces*

*Basidiobolus*

bone marrow transplantation

*Conidiobolus*

*Cunninghamella*

deferoxamine

diabetes mellitus

immunocompromised

ketoacidosis

mucormycosis

neutropenia

pneumonia

posaconazole

isavuconazole

*Rhizomucor*

*Rhizopus*

*Saksenaea*

sinusitis

zygomycosis

# Short View Summary

* 1. **Definition**
     + Mucormycosis is an aggressive, angioinvasive fungal infection, caused by filamentous fungi in the subphylum Mucoromycotina, order Mucorales, that afflicts immunocompromised patients with severe metabolic conditions, such as uncontrolled diabetes mellitus. Skin and soft tissue infections in immunocompetent patien hosts may be encountered in patients with severe soft tissue trauma (e.g., from tornadoes, combat injuries, or burns).
     + Entomophthoramycosis is a rare infection of the paranasal sinuses, subcutaneous tissues, or gastrointestinal (GI) tract caused by filamentous fungi in the subphylum Entomophthoramycotina that are principally encountered in the tropics.
  2. **Epidemiology**
     + Mucormycosis is acquired primarily via inhalation of environmental sporangiospores in immunocompromised hosts or through direct inoculation during trauma. The infection may break through antifungal prophylaxis regimens used to reduce the risk of aspergillosis.
     + Entomophthoramycosis typically is an indolent subcutaneous infection localized to the sinuses, head and face (conidiobolomycosis), or trunk and arms (basidiobolomycosis) and acquired by inhalation or minor trauma. GI basidiobolomycosis has occurred in Arizona and the Near East and is perhaps acquired by ingestion.
  3. **Microbiology**
     + Most common culture-confirmed cases reported in the literature are *Rhizopus* spp. (47%), *Mucor* sp. (18%), *Cunninghamella bertholletiae* (7%), *Apophysomyces elegans* (5%), *Lichtheimia (Absidia)* spp. (5%), *Saksenaea* spp. (5%), and *Rhizomucor pusillus* (4%), with other species (8%) accounting for the remaining cases.
     + *Conidiobolus coronatus* and *Conidiobolus incongruous* cause conidiobolomycosis. *Basidiobolus ranarum* causes basidiobolomycosis.
  4. **Diagnosis**
     + A high index of suspicion in immunocompromised patients is essential because most signs, symptoms, and radiographic signs of mucormycosis are nonspecific. Cultures have poor sensitivity. Diagnosis is typically established by histopathologic documentation of “ribbon-like” angioinvasive hyphae in tissue, although this is prone to error.
  5. **Treatment**
     + Lipid formulations of amphotericin B are the drugs of choice. Oral posaconazole, or perhaps isavuconazole, is used for treatment once infection is clinically stable and if absorption is adequate.
  6. **Prevention**
     + Given the rarity of mucormycosis and entomophthoramycosis, primary prophylaxis is not recommended. Secondary or potentially indefinite prophylaxis should be considered for immunocompromised patients with a previous episode of mucormycosis, depending on the status of underlying immunosuppression.

The disappearance of the class Zygomycetes from current taxonomy has made the term *zygomycosis* obsolete. The term *zygomycosis* encompassed both mucormycosis and entomophthoramycosis. These two infections are so different that no new name has been proposed to include both infections. Most of this chapter discusses mucormycosis, a group of filamentous fungi in the subphylum Mucoromycotina that belong to the order Mucorales. Mucorales can cause life-threatening infections in humans, especially in immunocompromised hosts. The first documented report of human mucormycosis is credited to Paltauf,1 who in 1885 reported a disseminated infection in a patient with rhinocerebral involvement caused by angioinvasive, ribbon-like hyphae that he termed *Mycosis mucorina*. Subsequent descriptions of the infection in the following decades relied on tissue morphology and, as often is the case today, were infrequently confirmed by culture. Hence the findings of coenocytic (aseptate or pauciseptate) fungal hyphae in tissue invading blood vessels was assumed to be due to *Mucor* spp. and have become synonymous with the clinical term *mucormycosis* or, simply, *Mucor* infection. This terminology is further justified by the fact that all but the rare *Mortierella* spp. are within the order Mucorales.2 However, the number of species causing human mucormycosis has expanded considerably in the past 2 decades with improvements in culture-based morphologic identification and the application of more precise molecular diagnostics and sequencing for fungal identification (Table 258.1). In fact, members of the genus *Rhizopus,* not *Mucor,* are reported as the most predominant cause of human infections, although in Europe *Mucor* and *Lichtheimia* account for approximately one-quarter of reported cases.3–5

# Etiology

Agents of mucormycosis are ubiquitous fungi in the environment that are commonly found in decaying organic substrates, including bread, fruits, vegetable matter, soil, compost piles, and animal excreta.6 These fungi characteristically produce large, ribbon-like hyphae that are irregular in diameter with only occasional septae, hence the characterization of these organisms as aseptate fungi. Identification can be confirmed by observing the characteristic, saclike fruiting structures (sporangia), which produce internally spherical yellow or brown spores (sporangiospores) (Fig. 258.1).6 Spores ranging from 3 to 11 µm in diameter are easily aerosolized and dispersed and cause infections in humans when inhaled or introduced through a cutaneous or percutaneous route.6

Although several species of the order Mucorales have been reported to predominate as causes of human mucormycosis, culture recovery of these fungi from infected tissue is suboptimal and may skew the current understanding of the etiologic spectrum of mucormycosis. The widening application of molecular diagnostic techniques (i.e., polymerase chain reaction [PCR]) in culture-negative cases may expand the current understanding of the prevalence and etiology of this infection. In a global review of more than 900 reported cases of mucormycosis, *Rhizopus* spp. (47%) were the most frequently reported causes of culture-confirmed mucormycosis, followed by *Mucor* spp. (18%), *Cunninghamella bertholletiae* (7%), *Apophysomyces elegans* (5%), *Lichtheimia (Absidia)* spp. (5%), *Saksenaea* spp. (5%), and *Rhizomucor pusillus* (4%), with a variety of other uncommon species representing the remaining 8% of culture-confirmed cases.3

Seasonal variations may affect the incidence of mucormycosis, with most infections occurring during periods of higher temperatures and decreased precipitation.**7**,8 Likewise, major weather events have also been associated with infections with less frequently isolated species, such as *Syncephalastrum racemosum* from respiratory samples after Hurricane Katrina, *Apophysomyces trapeziformis* soft tissue infections in patients with traumatic injuries associated with the Joplin, Missouri tornado,9 or posttsunami wound infections due to *Apophysomyces elegans.*10 Combat wound infections are also influenced by environmental factors, as in Afghanistan, where wounds sustained in the southern regions, with lower elevation, warmer temperatures, and greater isothermality, had greater mold contamination.**11**

## Insights From Genomic Sequencing

The first published genomic sequence of an agent of mucormycosis was *Rhizopus arrhizus* strain 99-880 (subsequently reclassified as *Rhizopus delemar*), which was isolated from a diabetic patient with fatal cerebral mucormycosis.12 Sequencing revealed the presence of abundant transposable elements accounting for 20% of the genome and evidence of a whole-genome duplication event during the evolution of the fungus.12 The whole-genome duplication event resulted in duplication of nearly all subunits of the protein complexes involved in respiratory electron transport chains and ubiquitin-proteasome systems, as well as multiple gene families related to cell growth and signal transduction and known fungal virulence factors, including secreted aspartic and subtilase protein families.13 Sequencing also revealed duplication of the ergosterol biosynthetic pathway (e.g., lanosterol 14α-demethylase), the major target of azoles including voriconazole, isavuconazole, and posaconazole.14 These genetic features may explain why Mucorales have a uniquely aggressive capacity for rapid growth in patients, even in the face of exposure to antifungal agents and the host immune response.15 More recent sequencing studies of representative isolates from Mucorales and noninvasive Entomophthorales have identified differences in gene copy numbers that encode spore coat (Cot[H]) proteins, which facilitate invasion of blood vessel endothelial cells.**16** The most commonly isolated Mucorales (*Rhizopus, Mucor,* and *Lichtheimia*) contain three to seven copies of the *cotH* gene*,* whereas those that occasionally cause disease in humans (*Apophysomyces, Cunninghamella, Saksenaea,* and *Syncephalastrum*) contain only one to two copies. Notably, the *cotH* gene was lacking in Entomophthorales, which are taxonomically similar to Mucorales but do not cause blood vessel invasion.**16**

## Acquisition of Infection

The primary mode of acquisition of mucormycosis is inhalation of spores from environmental sources.**17** Trauma, penetrating wounds, burns, and direct injection of sporangiospores can cause infection through a cutaneous or percutaneous route. Gastrointestinal (GI) mucormycosis, although less common, has been reported in both immunocompetent and immunocompromised patients with repeated ingestion of spores during periods of severe malnutrition, ingestion of nonnutritional substances (pica), ingestion of contaminated pharmaceutical products, prepackaged foods, fermented porridges and alcoholic drinks prepared from corn, or eating with contaminated chopsticks.18,19 More recently, an outbreak of food poisoning was linked to intake of Greek yogurt contaminated with *Mucor circinelloides.*20 It is unclear whether the fungus itself, which could survive transit through the GI tract and retain virulence, or a secondary metabolite or toxin was the cause of clinical symptoms experienced by the consumers.

## Patient Populations at Risk

Agents of mucormycosis are unique among filamentous fungi in their ability to infect a broader, more heterogeneous population of human hosts compared with other opportunistic molds. The epidemiology of mucormycosis is similar in adult and pediatric patients.**21** Although most cases of mucormycosis are community acquired, nosocomial acquisition or pseudooutbreaks**22** have been linked to contaminated bandages and bandage tape,**23**–25 needles,26,27 and tongue depressors used to construct splints for intravenous (IV) and arterial cannulation sites in preterm infants.28,29 An outbreak of invasive mucormycosis in a pediatric hospital was linked to contaminated bed linens resulting from improper storage, packaging, and transport from an offsite laundry service.**23**,30

The populations most commonly at risk for mucormycosis include patients with poorly controlled diabetes mellitus, prolonged neutropenia, high-dose corticosteroid treatment,31,32 or immunosuppressive therapy associated with transplantation, and/or elevated levels of free iron, which enhances fungal growth.33 The importance of iron overload in the pathogenesis of mucormycosis was first noted in patients with end-stage renal disease in the preerythropoietin era, where regular transfusions were required for persistent anemia, resulting in iron overload.34 Treatment of these patients with deferoxamine to lower their iron levels was linked to the development of disseminated, rapidly fatal mucormycosis.35,36 It was subsequently discovered that although deferoxamine is an iron chelator for the human host, it also acts as a siderophore in Mucorales, directly delivering iron to the fungus.34 Less commonly, mucormycosis is a cause of infection in the setting of renal failure, diarrhea, and malnutrition in low-birth-weight infants and rarely in human immunodeficiency patients.3

Patients who develop mucormycosis in the absence of underlying disease or immunosuppression at the time of infection frequently have histories of penetrating trauma, burns, surgery, or illicit IV drug use before the infection. For example, a case series of mucormycosis at a nononcology, tertiary care center found that traumatic wounds or surgical sites were the most common infection sites (31%), followed by rhinocerebral (25%) and disseminated (12.5%) infections.37 Severe soft tissue infections from blast injuries in combat have also caused mucormycosis.37,38

Mucormycosis is infrequently identified as a complication associated with primary immunodeficiency. This complication has occurred in a case of severe congenital neutropenia associated with HAX-1 (HCLS1 [hematopoietic cell-specific Lyn substrate 1]–associated protein X-1) deficiency, or with a newly identified genetic abnormality, such as in a patient with a STAT-1 (signal transducer and activator of transcription-1) gain-of-function mutation who presented with disseminated *Apophysomyces trapeziformis* infection.39,40

## Incidence of Mucormycosis

Mucormycosis is not a reportable disease. The incidence of mucormycosis is probably underestimated in many epidemiologic series given the inherent challenges associated with antemortem diagnosis and the declining rate of autopsies in high-risk populations. A recent estimate of the disease burden of mucormycosis in US hospitals from 2005–15 reported a prevalence of 0.12 to 0.16 cases per 10,000 discharges, depending on the International Classification of Diseases–9 code definitions used to define the disease.**41** Cases of mucormycosis were associated with an average hospital length of stay of 17 days, with 23% dead at discharge and more than one-third of patients requiring readmission to the hospital. The average cost per hospital stay was $112,419 (2014 US dollars).**41** Surveys from Europe have reported incidence rates of mucormycosis ranging from 0.43 to 1.2 cases per million people.42,43 In autopsy series of high-risk hematology populations, mucormycosis has accounted for 8% to 13% of all reported invasive fungal infections.44–46

Mucormycosis is an important cause of fungal infections in patients with hematologic malignancy, recipients of allogeneic hematopoietic stem cell transplant (HSCT), and, less commonly, patients undergoing solid-organ transplantation (SOT) (Fig. 258.2).47 Data from the Centers for Disease Control and Prevention (CDC) Transplant-Associated Infection Surveillance Network (TRANSNET) acquired from prospective surveys of 25 US transplantation centers from 2001–06 reported 1-year cumulative incidence rates for mucormycosis of 0.29% in allo-HSCT and 0.07% in SOT,45,48 accounting for 8% and 2%, respectively, of fungal infections diagnosed in these populations. Of concern, some mucormycosis cases have presented as breakthrough infection on antifungal prophylaxis or treatment effective against *Aspergillus* but not Mucorales (i.e., voriconazole, echinocandins)49 or because of potentially insufficient absorption of posaconazole.50,**51** Collectively, these data suggest that mucormycosis should be considered in any high-risk hematologic malignancy patient whenever fungal sinusitis develops on *Aspergillus-*active antifungal prophylaxis, especially in patients with prolonged immunosuppression and underlying hyperglycemia associated with prolonged corticosteroid use.

# Pathogenesis (Fig. 258.3)

Most Mucorales sporangiospores are sufficiently small to evade host upper airway defenses and reach the distal alveolar spaces after inhalation.6 Larger spores (>10 µm) may lodge in the nasal turbinates, predisposing patients to sinusitis.6 Inhalation of a high spore inoculum, which can occur with excavation, construction, or work in contaminated air ducts, can lead to a slowly progressing pulmonary mucormycosis even in immunocompetent hosts.52,53 In the case of primary cutaneous mucormycosis, subcutaneous inoculation of spores is the most common event leading to infection in immunocompetent hosts. Cutaneous mucormycosis in immunocompetent hosts usually follows massive soft tissue injury but has been described with even minor trauma, including insect bites54 and tattoos.47

Relatively little is known about initial steps of how Mucorales sporangiospores attach to the respiratory or GI epithelium.**55** *Rhizopus* sporangiospores can adhere to extracellular matrix proteins, such as laminin and type IV collagen,56 which may be exposed after epithelial damage caused by cytotoxic chemotherapy, infection, diabetes, or trauma. Toxins elicited by Mucorales during germination may contribute to epithelial cell damage.57 A recent outbreak of food poisoning linked to intake of Greek yogurt contaminated with *M. circinelloides* identified secondary metabolites produced by the contaminating strain that were toxic to the GI mucosa.20

Mucorales appear to possess a unique mechanism for adhering to and invading endothelial cells by specific recognition of host receptor–glucose regulator protein 78 (GRP78).58 Expression of GRP78 on the endothelial cell surface increases as a stress response after exposure to elevated concentrations of β-hydroxy butyrate (BHB), glucose, and iron, similar to those found in patients with diabetic ketoacidosis.**59** Mucorales germlings, but not sporangiospores, bind to GRP78, initiating endothelial cell–mediated fungal endocytosis, resulting in host cellular death.58 Suppression of GRP78 expression or blocking its function by antibodies suppresses fungal invasion of host endothelial cells by Mucorales, but not *Aspergillus fumigatus* or *Candida albicans*.58 Endothelial cell uptake is also enhanced through activation of host platelet-derived growth factor pathways (PDGF)**16** because treatment with small-molecule inhibitors of PDGF reduces endothelial cell damage caused by *Rhizopus*.

Proteins from the CotH spore protein coat family are the key ligands that bind GRP78 expressed on the host endothelium.60 Blocking CotH protein function with antibodies reduces the ability of Mucorales to invade and injure endothelial cells in vitro and improves survival in mice.60 However, it is still unknown whether some hosts may be more susceptible to developing mucormycosis due to single nucleotide polymorphisms in GRP78, which could result in enhanced binding affinity for certain sequences of CotH proteins expressed in specific Mucorales.**61**

## Role of Iron Uptake in Mucormycosis Pathogenesis

Anecdotal case reports and experimental data from the 1980s suggested that hemochromatosis is a predisposing risk factor for mucormycosis.33,62 Fungi can acquire iron from the host by using low-molecular-weight iron chelators (siderophores) or high-affinity iron permeases, such as ferrirhizoferrin.63 Of the two mechanisms, it is believed that high-affinity iron permeases play the more critical role for adaptive survival of the fungus in the human host. Iron overload in organs such as the liver has also been reported to enhance fungal virulence.64

Patients with diabetic ketoacidosis are particularly susceptible to developing rhinocerebral forms of mucormycosis, perhaps because of diminished capacity of transferrin to bind and sequester free iron at a pH less than 7.4.33,65 The growth of *R. arrhizus* is markedly different in sera collected from patients with diabetic acidosis compared with healthy control subjects. Artis and colleagues33,65 reported that normal human serum is not capable of supporting the growth of *R. arrhizus* even with the addition of free iron. However, under acidic conditions (pH < 7.4), the addition of exogenous iron markedly enhances the growth of *R. arrhizus* hyphae. Similarly, sera collected from patients with ketoacidosis supports exuberant growth of *R. arrhizus* without exogenous iron, provided the pH was maintained at less than 7.4, suggesting that acidosis disrupts the ability of transferrin to bind and sequester free iron.33,65

Historically, patients with severe hemochromatosis or aluminum toxicity received treatment with the metal chelator deferoxamine, which, paradoxically, is associated with increased susceptibility for developing disseminated mucormycosis.34,66 Subsequent experimental models demonstrated that *R. arrhizus* can use deferoxamine as a xenosiderophore to form the ferrioxamine complex, which will make iron available for use previously unavailable to the fungus.34,67 Specifically, *Rhizopus* can bind deferoxamine complexes and strip away free iron through a reductive process that allows intracellular uptake of free iron through the enzyme iron permease.62 Of interest, uptake of radiolabeled iron in the presence of deferoxamine is 8- to 40-fold lower in *Candida* and *Aspergillus* compared with *R. arrhizus,* suggesting this mechanism is a relatively unique pathogenic trait of this fungus. This observation has been confirmed in animal models where administration of deferoxamine worsens survival of guinea pigs infected with *R. arrhizus* but not *Candida albicans.*67

Unlike deferoxamine, newer iron chelator agents, such as deferiprone and deferasirox, have not been associated with increased risk for mucormycosis because of their limited capacity to act as xenosiderophores for *Rhizopus* spp. Indeed, both deferiprone and deferasirox have shown protective effects in murine68 and guinea pig66 models of mucormycosis, with several case reports suggesting a possible benefit of adjunctive deferasirox therapy in human mucormycosis.69 However, a small nonrandomized study found no survival benefit of adding deferasirox in combination with liposomal amphotericin B (L-AMB) in patients with hematologic malignancies.70 Deferasirox may be more effective adjunct therapy for mucormycosis in the setting of diabetic ketoacidosis versus patients with neutropenia. Nevertheless, adjunctive iron chelation therapy cannot be recommended in patients with mucormycosis until more convincing clinical evidence of its benefit is available.71

## Host Immune Response Against Mucormycosis

Both mononuclear and polymorphonuclear phagocytes, including natural killer cells, prevent germination of Mucorales spores and damage hyphal forms of the fungus.72–74 After encountering *R. arrhizus* hyphae, human polymorphonuclear neutrophils activate robust proinflammatory gene expression through activation of Toll-like receptor 2 and nuclear factor kappa B pathways.75 Hyphal damage is elicited by oxidative mechanisms after monocyte or neutrophil attachment to hyphal fragments.72,76 Platelets may also play a role in host antifungal defenses against Mucorales by adhering to hyphae forms and secreting microbiocidal proteins.77

Defects in phagocytic activity associated with decreased cell numbers (i.e., neutropenia) or function (i.e., associated with glucocorticoids, hyperglycemia, or acidosis) allow unimpeded growth of the hyphal form. Glucocorticoids are known to impair the migration, attachment, ingestion, and phagolysosome fusion of bronchoalveolar macrophages essential for clearing spores from the alveoli.78 Neutrophils collected from patients with severe hyperglycemia and diabetic ketoacidosis, burn-stress pseudodiabetes, or glucocorticoid-treated graft-versus-host disease (GVHD) often have impaired chemotaxis and diminished oxidative and nonoxidative fungicidal mechanisms against Mucorales spores and hyphae.79 In the setting of these impaired host immune defenses, rapidly growing Mucorales can outcompete the impaired immune response and rapidly spread through tissues and blood vessels.**55**

Mucorales-specific CD4+ or CD8+ T cells that produce interferon (IFN)-γ, interleukin (IL)-10, and, to a lesser extent, IL-17 can be detected early in infection in patients with hematologic malignancies and decrease with resolution of the infection.80 As such, detection of such cells may support the diagnosis of mucormycosis. Mucorales have also been reported to activate human dendritic cells through Dectin-1, resulting in the production of IL-23 and induction of proinflammatory Th17 responses.81 Elevated concentrations of glucose, iron, and BHB encountered in patients with diabetic ketoacidosis impair T-cell proliferation, IFN-γ production, and phagocyte-mediated killing.**59**,82–85

Evidence from animal models suggests that Mucorales can persist in granulomatous clusters, which reactivate during periods of intensive immunosuppression or metabolic dysfunction, such as diabetic ketoacidosis.86 The possibility of a preexisting latent infection stage raises questions concerning the possibility of screening for latent mucormycosis in patients before undergoing intensive immunosuppressive therapy.

## Histopathology

Mucorales have an exceptional capacity to invade blood vessels, resulting in necrosis of vessel walls and mycotic thrombi.87 Thrombosis of vessels leads to infarction and hematogenous dissemination. Infected tissue typically reveals extensive necrosis with diffuse infiltration of polymorphonuclear leukocytes. However, in areas with ischemic necrosis, inflammation is sometimes minimal despite the presence of numerous hyphae.88,89 In the otherwise healthy host a pyogenic or pyogranulomatous response without angioinvasion is more common. Reactivation from granulomas, that is, granulomatous inflammation, is possible during periods of subsequent immunosuppression or metabolic dysfunction (e.g., hyperglycemia, ketoacidosis).

# Clinical Manifestations of Mucormycosis

The clinical presentation of mucormycosis is broad, depending on the underlying immune status and comorbidities of the host (Table 258.2). The signs and symptoms of mucormycosis are nonspecific, emphasizing the importance of a high index of suspicion in susceptible patient populations. In the immunocompromised host, mucormycosis can present as a fulminant angioinvasive infection that frequently disseminates with fatal consequence. The clinical manifestations of mucormycosis can be generally grouped into one of six syndromes with some overlap: (1) rhinocerebral infections and (2) pulmonary, (3) cutaneous, (4) GI, (5) disseminated, and (6) unusual presentations of mucormycosis.

## Rhinocerebral Infections

Rhinosinusitis, rhino-orbital, and rhinocerebral infections are classic manifestations of human mucormycosis. Infection is initially localized to the nasal turbinates and paranasal sinuses after inhalation of spores but can rapidly progress to the orbit (sino-orbital) or brain (rhinocerebral), particularly in patients with diabetic ketoacidosis or profound neutropenia.42,90 Patterns of progression for the infection demonstrate some host predilection (see Table 258.2). The rhino-orbital form occurs more frequently in patients with poorly controlled diabetes, whereas patients with underlying leukemia or lymphoma are more likely to present with pulmonary infections (Fig. 258.4). Indeed, rhino-orbital mucormycosis is sometimes the first manifestation of undiagnosed diabetes mellitus, especially in patients from developing countries.

### Clinical Presentation

Initial symptoms of sinus invasion by mucormycosis are indistinguishable from other more common causes of sinusitis. Sinus pain, congestion, headache, mouth or facial pain, otologic symptoms, and hyposmia or anosmia are common. A concomitant nonproductive cough often reflects lung involvement. Involved tissues become red, then violaceous, and finally black with thrombosis and tissue necrosis. Necrotic eschars of the nasal cavity and turbinates, facial lesions around the nose, and exophytic or necrotic lesions of the hard palate extending from the maxillary sinus are signs of rapidly progressing infection.91 Careful endoscopic inspection of the nasal cavity and biopsy of suspicious lesions is helpful for early diagnosis. However, the absence of lesions or necrotic eschars does not rule out the possibility of rhinocerebral infection because necrotic nasal or palate lesions may be seen in only 50% of patients within 3 days of the onset of infection.91

Extension of sinus disease is primarily into contiguous structures. Maxillary sinus infection extends into the hard palate, nasal cavity, and ethmoid sinus. Sphenoid disease invades the cavernous sinus, contiguous temporal lobe, and internal carotid artery in the siphon. Septic emboli from the carotid artery into the frontal and parietal lobes can occur. Ethmoid sinus disease may invade the face or frontal lobe but easily crosses the lamina papyracea into the orbit.92 The frontal sinus is an uncommon primary site. Invasion of the orbit is typically unilateral (see Fig. 258.4). Periorbital edema, ptosis, proptosis, chemosis, and preseptal and orbital edema are early signs of orbital extension. Pain and blurring or loss of vision often indicate invasion of the globe or optic nerve. Infraorbital facial numbness follows invasion of the infraorbital nerve within the orbit.92 Patients with extensive rhino-orbital or rhinocerebral disease may present with trigeminal and ocular motor nerve palsy after cavernous sinus invasion (cranial nerves III, IV, and VI, and the superior two branches of the fifth nerve).93 A bloody nasal discharge may be an early sign of nasal mucosal invasion.94,95 Intracranial complications include epidural and subdural abscesses, cavernous, and, less commonly, sagittal sinus thrombosis.96–98 Frank meningitis in patients with mucormycosis is rare.**17**

### Radiology

Radiographic imaging is often suggestive of severe sinusitis but lacks the specificity to diagnose rhinocerebral mucormycosis. Patients with fungal or surgical disruption of the dura mater may present with superimposed bacterial meningitis, or bacterial sinusitis may complicate postoperative management.99 Computed tomography (CT) of the sinuses typically reveals mucosal thickening, air-fluid levels, and bony erosion (Fig. 258.5).100 Highly immunosuppressed patients often present with pansinusitis that is highly suggestive of an aggressive fungal infection.50 Orbital thickening may also be detected on CT scans but can be detected earlier by magnetic resonance imaging (MRI).101 CT and MRI scans of the orbits may be unremarkable during the initial stages of the infection, highlighting the importance of serial radiographic imaging for monitoring disease progression.101 The frequency of radiographic imaging is patient dependent but may be required every 2 to 3 days in patients with suspected progression. Therefore rhinoscopy or nasal endoscopy is critical for confirming tissue ischemia and the extent of disease.99 Extraorbital muscle thickening is often the first sign on CT or MRI of orbital involvement and should prompt empirical antifungal therapy until surgical exploration or biopsy of the sinus and orbits can be performed, which should be done as soon as possible.100 Every effort should be made to establish an early definitive diagnosis of mucormycosis by biopsy and culture of necrotic lesions and rapid histologic assessment of frozen sections.102 Impression smears from the biopsy or surgical margin may also reveal hyphae consistent with mucormycosis.

## Pulmonary Infections

Pulmonary mucormycosis is most commonly encountered in patients with prolonged neutropenia, recipients of hematopoietic stem cell or solid-organ transplantation, and patients receiving deferoxamine therapy.3,**17**,103 The infection frequently occurs concomitantly with sinus infection.**17** However, the clinical manifestations of the infection are indistinguishable from more common opportunistic molds, such as invasive pulmonary aspergillosis (IPA). Therefore timely diagnosis is a critical factor in the outcome on the infection because first-line antifungals typically used for aspergillosis, such as voriconazole, lack activity against Mucorales. A case series of 61 leukemia and transplant patients with evidence of fungal pneumonia found that 84% of patients who were eventually documented to have pulmonary mucormycosis were receiving ineffective antifungal therapy at the time of their diagnosis.**104**,105 Similarly, an analysis of 70 hematologic malignancy patients with pulmonary mucormycosis demonstrated that a delay in the administration of appropriate antifungal therapy (typically an amphotericin B formulation) of as few as 6 days was associated with a doubling of 4-week (35.1% vs. 66.6%; *P* = .006) and 12-week (48.6% vs. 82.9%; *P* = .029) crude mortality rates.106 Data to support imaging findings that might heighten the suspicion for pulmonary mucormycosis are reported in a retrospective analysis of neutropenic leukemia patients. In the first 5 days of clinical symptoms, fever or chest pain, a reverse halo sign (focal ground-glass attenuation surrounded by a ring of consolidation) was present in 15 of 16 patients with proven pulmonary mucormycosis.**107**,108 However, the reverse halo sign is not specific for mucormycosis but, rather, may be suggestive of invasive aspergillosis, mucormycosis, or organizing pneumonia.109,109a

### Clinical Presentation

Clinical symptoms of pulmonary mucormycosis are subtle and nonspecific even at late stages in the infection, especially in patients receiving therapies that suppress immune responses (i.e., high-dose glucocorticoid therapy, anti–T-cell antibodies).106 Patients frequently present with refractory fever on broad-spectrum antibiotics, nonproductive cough, progressive dyspnea, and pleuritic chest pain.50,106 Pulmonary mucormycosis can traverse tissue planes in the lung, invading through the bronchi, diaphragm, chest wall, and pleura.103 A pleural friction rub on auscultation is present in some patients. Hyphal invasion of blood vessels results in necrosis of the surrounding parenchyma, ultimately leading to cavitation or potentially fatal hemoptysis.110–112 In patients with hematologic malignancies, clues for distinguishing pulmonary mucormycosis from IPA may include the presence of severe sinusitis; history of prophylaxis with antifungals that possess activity against aspergillosis but not mucormycosis (i.e., voriconazole or echinocandin prophylaxis); suggestive CT imaging findings, such as reverse halo sign and multiple nodular infiltrates with or without pleural effusion; and possibly the repeated absence of detectable *Aspergillus* galactomannan antigen in the serum or in bronchial alveolar lavage (BAL) fluid.50,**113**–115 Unfortunately, it is common in debilitated patients to have a concomitant polymicrobial pneumonia, which can further confound early diagnosis of pulmonary mucormycosis.103,110

### Radiology

The radiographic presentation of pulmonary mucormycosis is broad, including focal consolidation with nonspecific infiltrates, cavitary lesions, or even diffuse opacities that evolve quickly, depending on the underlying immune status of the patient (see Fig. 258.5).103,**116** Thrombosis of pulmonary vessels with angioinvasion often leads to large wedge-shaped infarcts.103 Earlier studies of pulmonary mucormycosis suggested a predilection for upper lobar disease in 55% to 84% of cases.117,118 However, any part of the lung may be involved, and bilateral disease is common**.**103

Like IPA, high-resolution chest CT is the best method of determining the extent of pulmonary mucormycosis and typically demonstrates evidence of the infection before its appearance on standard chest radiographs (see Fig. 258.5). Although nodular opacities without an air bronchogram indistinguishable from aspergillosis are the most common finding on CT scan, the presence of multiple nodules (≥10), pleural effusion, or both, may favor the diagnosis of pulmonary mucormycosis.**116** Halo and air crescent signs are encountered less frequently in leukemic patients with pulmonary mucormycosis compared with pulmonary aspergillosis.**116** However, centrally located lesions demonstrating the air-crescent sign are often associated with an increased risk for pulmonary artery erosion and massive hemoptysis.102 Three small case series have suggested that a reverse halo sign, a focal round area of ground-glass attenuation surrounded by a ring consolidation, may be a more common early radiographic finding in patients with invasive pulmonary mucormycosis compared with aspergillosis.**107**,108,119,120

Pulmonary mucormycosis rapidly spreads to the contralateral lung and distal organs if not promptly treated. Although patients with pulmonary mucormycosis usually die from disseminated disease before respiratory failure occurs, dissemination is rarely detected antemortem.121 The overall mortality rate of pulmonary mucormycosis ranges from 50% to 70% but can increase up to 95% in patients with extrathoracic dissemination.121

# Pulmonary Mucormycosis in Less Severely Immunocompromised Patients

In more immunocompetent hosts, pulmonary mucormycosis may present with more atypical, slowly progressing forms.6 Mycotic pulmonary artery aneurysms and pseudoaneurysms, bronchial obstruction, and even asymptomatic solitary nodules have been described without clear underlying immune dysfunction. Patients with diabetes mellitus have a predilection for developing endobronchial lesions that present with a less fulminant course than pulmonary mucormycosis encountered in the neutropenic or transplant population.117 On occasion, endobronchial lesions may lead to obstruction of the major airways or erosion of major pulmonary blood vessels and fatal hemoptysis.

Like *Aspergillus* spp., Mucorales in rare instances can form mycetomas in preexisting lung cavities or cause slowly necrotizing pneumonia and hypersensitivity syndromes. *Rhizopus* spp. have also been implicated in an allergic alveolitis described in farm workers and Scandinavian sawmill workers (wood-trimmer's disease).122,123

## Skin and Soft Tissue Infections

Cutaneous mucormycosis is typically the result of direct spore inoculation or exposure of skin already compromised by burns or extensive trauma or, less commonly, after insect or spider bites.124,**125** Necrotizing soft tissue infections with cutaneous mucormycosis have been reported in survivors with traumatic injuries after volcanic eruptions, tsunamis, and tornadoes.9,10 Mucorales-contaminated bandages, needles, and bed linens have also been implicated in outbreaks of soft tissue infections in hospitalized patients.**23**–27,30

Cutaneous mucormycosis typically starts as erythema and induration of the skin at a puncture site and progresses to necrosis with a black eschar (Fig. 258.6). Cutaneous infections can quickly extend into the deep fascia and muscle layers. Necrotizing fasciitis has been reported in patients with progressive cutaneous mucormycosis and is associated with an extremely poor prognosis.126–131 Neutropenic patients, in particular, are susceptible to lymphatic and blood vessel invasion, infarction, and necrosis with eventual dissemination. In patients with massive soft tissue trauma the mold invades the gray necrotic tissue at the margins of the wound and spreads to contiguous viable tissue, enlarging the wound. Unlike many other molds (*Aspergillus, Fusarium, Scedosporium,* fungi causing phaeohyphomycoses), the skin appears to be a less common site of secondary involvement in disseminated mucormycosis.**17** Atypical dermatologic manifestations have also been reported in less immunosuppressed leukemic patients and solid-organ transplant recipients, mimicking erythema nodosum or panniculitis.132,133

Skin biopsy is critical for diagnosis because necrotic skin lesions in neutropenic patients have a broad differential diagnosis.134 Biopsy specimens taken from the center of the lesion down to the subcutaneous fat are most likely to reveal hyphae invading the blood vessels of the dermis and subcutis. Excision and wide débridement of cutaneous lesions, coupled with systemic antifungal therapy and, according to some, hyperbaric oxygen therapy, can further reduce mortality rates (see Chapter 50).

## Osteomyelitis

Mucorales are an uncommon cause of bone and joint infections that are typically diagnosed late after initial symptom onset. A review of 34 individual cases from 30 publications**135** found that bone and joint infections were most frequently associated with trauma, automobile accidents with fracture, and puncture of the knee or penetrating wounds. Direct inoculation was the main mechanism of infection in 56% of cases, particularly in patients with prior trauma or surgery. Hematogenous dissemination occurred in 24% of cases in patients with hematologic malignancy or immune impairment, whereas another 21% of cases occurred from contiguous spread of the infection. Fever was uncommon, but patients frequently experience local pain and tenderness in the affected joint with occasional cellulitis with elevated inflammatory markers, such as elevated erythrocyte sedimentation rate, white blood cell counts, and possibly elevated C-reactive protein. Diagnosis was most frequently established by open surgical biopsy.**135** Mucorales osteomyelitis requires both antifungal treatment and surgical intervention that may include débridement, bone grafting/fixation procedures, full excision, or amputation if required. The overall mortality rate in a published case series was 24%.**135**

## Gastrointestinal Mucormycosis

Primary GI mucormycosis is a rare infection, with protean manifestations occurring primarily in malnourished patients and premature infants, where it can present as necrotizing enterocolitis.19 The infection often starts with an ulcer, sometimes in the stomach, but can involve any compartment of the GI tract.136 Patients may present with peritonitis after the fungus has invaded through the gastric mucosa and bowel wall.137 Liver abscesses have also been described after ingestion of herbal products contaminated with *Mucor indicus.*138 In neutropenic patients seeding of the GI tract is probably more common than previously thought because only a few of the infections are identified antemortem. Patients may present with subtle findings of fever, enterocolitis, or hematochezia that can progress to colonic ischemia with transmural necrosis and perforation of the gut. Masslike appendiceal or ileal lesions have also been described.137 Unfortunately, GI mucormycosis is often diagnosed late because of the nonspecific presentation and a high degree of suspicion is required for early diagnosis by endoscopic biopsy.137

## Disseminated Mucormycosis

Disseminated mucormycosis is rarely apparent before death. The symptoms vary depending on the site of dissemination, degree of vascular invasion, and affected organs. The patient groups classically at risk for this infection have received treatment with deferoxamine for iron overload, are persistently neutropenic patients with active leukemia, or are allogeneic stem cell transplant recipients with GVHD receiving high-dose glucocorticoid therapy or anti–T-cell antibodies.6,**17** Pneumonia is common in patients with disseminated mucormycosis and is assumed to be the primary source in most patients even when not detectable radiologically.121 Because of the poor sensitivity of blood and respiratory cultures for diagnosing disseminated mucormycosis, biopsy of the suspected sites is critical for diagnosis of the infection. Patients with hematologic malignancies or diabetic patients with disseminated mucormycosis have presented with acute myocardial infarction or bowel ischemia after arterial occlusion by fungi.139–141

## Less Common Presentations of Mucormycosis

Although rare, peritonitis has been described in patients undergoing continuous ambulatory peritoneal dialysis.142–144 The infection tends to have a slowly progressive course, although the attributable mortality rate in patients who received delayed or inappropriate therapy can exceed 60%.142 In peritoneal dialysis, catheter-related mucormycosis, prompt removal of the catheter, and several weeks of systemic antifungal therapy are essential.

Isolated reports of mucormycosis of the trachea,145 mediastinum,146 bone,147 heart,148,149 thyroid, and kidney150 have been described. Other manifestations, such as otitis externa,151 corneal infection, and superior vena cava syndrome,152 have also been reported. IV drug abusers are particularly vulnerable to central nervous system manifestations of mucormycosis, often presenting as a brain abscess involving the basal ganglia in conjunction with infective endocarditis.153–157

# Diagnosis

Because of the ubiquitous nature of the fungus in the environment, positive cultures may occasionally reflect culture contamination rather than true infection. However, discovery of hyphae in a specimen from an immunocompromised host is an important diagnostic clue that should be confirmed whenever possible with histopathologic documentation of fungal invasion.158 Not surprisingly, the site of infection has a major impact on the likelihood of histopathologic confirmation.6 The ease of accessibility of the skin or sinuses allows more definite diagnosis of infections at these sites. Tissue swabs and cultures of sputum, sinus secretions, nasal mucosa, and BAL fluid are usually nondiagnostic but may be an important indication of disease in immunocompromised patients.159 Blood cultures rarely grow Mucorales despite the angioinvasive nature of these pathogens.

In tissue, Mucorales hyphae can often be distinguished from other more common opportunistic molds, such as *Aspergillus* and *Fusarium,* by their broad (uneven diameter, 3–25 µm), empty, thin-walled, mostly aseptate hyphae.87 Frequently, these hyphae have focal bulbous dilation and nondichotomous irregular branching at occasional right angles. Tissue sections may show a variety of mixed hyphal forms that include folded, twisted, or compressed hyphae that may be mistaken for septae or, when transected, large empty spherules of *Coccidioides immitis.* Reproductive hyphal structures containing spores (sporangia) are rarely observed in deep tissue, even in well-aerated sites of infection. Mistaken histologic identification is relatively common and can lead to inappropriate therapy.

A variety of stains, including hematoxylin and eosin, Grocott-Gomori methenamine silver, and periodic acid–Schiff stains, will reveal characteristic hyphal elements in tissue. Failure of hyphae to stain with Grocott-Gomori methenamine silver is observed in some patients. Perineural invasion is found in 90% of tissues that contain nerves.93 The inflammatory process can range from neutrophilic, granulomatous, or pyogranulomatous to minimal inflammation with hemorrhage, depending on the degree, chronicity, and type of underlying immune deficit.87 Fungal hyphae can also be examined directly with a potassium hydroxide preparation of the tissue specimen or BAL fluid. Staining with fluorescent dyes, such as calcofluor white, Blankofluor, or Uvitex, may enhance detection of hyphal elements during ultraviolet microscopic examination and improve the discrimination between septate and aseptate molds in biopsy specimens.**104**,105,160

## Species Identification

Identification of Mucorales to the genus and species level requires cultivation of the fungus in culture to examine reproductive fruiting structures of the fungus. Most species grow rapidly on fungal media, such as Sabouraud dextrose agar incubated at 25° to 30°C. The level of development of the rhizoids, the shape of the sporangium, and the location of the sporangiospores are the morphologic features used to identify different genera of Mucorales (see Fig. 258.1). Nucleic acid sequencing of PCR is being used increasingly to identify cultures without typical morphologic features.161 Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry may also aid identification and is becoming more available in reference laboratories, although reference databases used to aid interpretation are still limited.**162**,**163** Recent applications of PCR-based identification have suggested that up to 20% of species may be misidentified at the species level by morphology alone. Unfortunately, culture recovery of the agents of mucormycosis from tissue is inherently poor owing to the friability of the nonseptated hyphae, making them more susceptible to damage during tissue manipulation. Recovery from tissue can be improved by mincing (not homogenizing) tissue and using culture techniques that simulate in vivo growth, including incubation at 35° to 37°C in semianaerobic conditions.164,165

## Differentiating Mucormycosis From Other Molds

The importance of early differentiation of mucormycosis from other mold infections has generated interest in the development of non–culture-dependent or non–histopathology-dependent diagnostic tests, such as detection of specific antigens or nucleic acid by PCR. Unfortunately, molecular techniques are in use only in research laboratories for the diagnosis of mucormycosis but have shown some promise when evaluated retrospectively in histopathologic or culture-confirmed cases.166,**167** Antigen tests for *Aspergillus* (galactomannan) and other fungal species (β-d-glucan) are not useful for mucormycosis. Several studies have attempted to improve early diagnosis through detecting nucleic acid in serum by using PCR assays or in situ hybridization techniques.161,**168**–170 To date these techniques have shown the greatest utility as adjunctive diagnostics, for molecular typing in epidemiologic studies, or for confirming the presumptive genus of the pathogen when histopathology is positive, but cultures are negative.171 In a prospective study of CT-guided percutaneous lung biopsy samples from nonthrombocytopenic patients with suspected fungal pneumonia, Lass-Florl and colleagues105 demonstrated that the rapidity of diagnosis and differentiation of mucormycosis from aspergillosis could be improved by using a three-step analysis approach for biopsy specimens: (1) calcofluor white staining to rapidly distinguish septate versus aseptate hyphae, (2) *Aspergillus* galactomannan and PCR testing for rapid identification, and (3) PCR testing of DNA in select biopsy specimens in which aseptate hyphae were observed or *Aspergillus* markers were negative. These promising results will require further confirmation in a wider range of patients before PCR becomes a standard-of-care adjunctive diagnostic test for mucormycosis.

## Antifungal Susceptibility Testing

Susceptibility testing of Mucorales isolates is not routine in most clinical microbiology laboratories. Although standardized methods applicable for testing Mucorales isolates have been proposed by both the Clinical Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST), minimal inhibitory concentration (MIC) results obtained using these two methods often differ.**172**,**173** Moreover, MIC results often increase by at least two dilution steps with incubation beyond 24 hours.**174** Agar-based methods, such as the Etest, have shown relatively good reproducibility and agreement (70%–100%) with broth microdilution methods, depending on the isolate and Mucorales tested.175 Nevertheless, the performance of many commercially available tests has not been systematically compared with reference methods for Mucorales. Interpretive MIC breakpoints have not been defined for the Mucorales. Therefore the role of MIC testing in the management of mucormycosis remains uncertain.

Amphotericin B is considered the most active drug against Mucorales and is active in vitro against most species within this order with MIC values of 0.03 to 2 µg/mL (Table 258.3).**174** However, susceptibility does vary by species, with higher MICs observed for *Cunninghamella* spp.**176** Epidemiologic cut-off values (ECVs) for amphotericin B have been proposed using CLSI methods for *Lichtheimia corymbifera*, *M. circinelloides,* and *Rhizopus microsporus* (2 µg/mL) and for *R. arrhizus* (4 µg/mL).**176** The frequency of non–wild-type isolates based on these ECVs ranges from 0%–2.15% depending on the species. One small case series reported that Mucorales infections associated with an amphotericin B MIC <0.5 µg/mL was significantly associated with better 6-week outcomes.**177**

Posaconazole and, perhaps, isavuconazole are considered to have clinically useful anti-Mucorales activity (see Table 258.3). The MIC50 of posaconazole ranges from 0.25 to 2 µg/mL for *Rhizopus* spp., 0.5 to 2 µg/mL for *Mucor* spp., and 0.125 to 1 µg/mL for *Lichtheimia* spp.**172**,**173**,178 When evaluated in neutropenic murine model of invasive pulmonary mucormycosis, the posaconazole serum area under the concentration-time curve (AUC)/MIC ratio was most predictive of antifungal effect, with the greatest reduction in lung fungal burden measured at an AUC/MIC greater than 100.179 For *R. arrhizus* (MIC, 2 µg/mL), an AUC/MIC target >100 was achieved when serum trough posaconazole exposures in the animals exceeded 4 µg/mL.179

Isavuconazole susceptibility is species dependent, with MIC50s ranging from 0.25 to 1 µg/mL for *Lichtheimia* spp. and *Rhizomucor* spp., 1 µg/mL for *Rhizopus* spp., but significantly higher for *M.* circinelloides (8 µg/mL).**172** Although MICs in general are one to three dilutions higher for isavuconazole versus posaconazole, slightly higher serum drug exposures with isavuconazole might possibly compensate for these modest differences in potency.**172**

Itraconazole exhibits variable species-specific antifungal activity in Mucorales, similar to isavuconazole, but itraconazole's unpredictable absorption does not make it a reliable triazole for treatment of invasive mucormycosis. Fluconazole lacks activity against Mucorales (see Table 258.3), and voriconazole lacks sufficient activity in vitro and in vivo to treat mucormycosis at clinically achievable concentrations.**172**,**173**,178 The lack of sufficient voriconazole activity in vivo is also reflected by frequent cases of breakthrough mucormycosis in patients on voriconazole prophylaxis or therapy.**51**,115,121

Although 1,3-β-d-glucan synthase target is present in Mucorales, 1000-fold higher echinocandin concentrations are required to inhibit the enzyme complex in *R. arrhizus* compared with *Candida albicans* or *Aspergillus fumigatus*.180 In consequence, echinocandins are not considered effective agents in vivo and have demonstrated only limited activity in animal models as monotherapy at lower but not higher doses.180–182

## Combination Therapy

In vitro and preclinical in vivo studies of antifungal combination therapy (lipid amphotericin B formulations, triazoles, echinocandins, flucytosine, and terbinafine, as well as non-antifungal agents) have revealed mostly indifferent interactions with occasional synergy but no reports of antagonism for combinations of triazoles, amphotericin B, echinocandins, terbinafine, and, on occasion, non-antifungal agents.**174**,183 A combination of lipid amphotericin B plus an echinocandin demonstrated improved survival in *R. arrhizus* rodent infection models compared with lipid amphotericin B alone.181,184 Combinations of posaconazole or isavuconazole with either echinocandins or lipid amphotericin B formulations generally display indifferent results with respect to either triazole or lipid amphotericin B monotherapy.**174**,**185**,**186**

Deferasirox, the iron chelator with antifungal effects against Mucorales, has been evaluated in combination with L-AMB68 and in triple combination with micafungin.184 Both of these combination regimens, which were administered in diabetic mice, were more effective at prolonging survival compared with L-AMB alone. Modest synergistic effects were also noted in a neutropenic murine models of *R. arrhizus* invasive pulmonary mucormycosis with a combination of posaconazole and deferasirox.179 However, combination regimens (posaconazole plus L-AMB, posaconazole plus an echinocandin, or posaconazole plus deferasirox) were only as effective as maximally dosed posaconazole.179 Nevertheless, when deferasirox combined with L-AMB was evaluated in a double-blind multicenter study of neutropenic patients with mucormycosis, no survival benefit was found in the combination therapy group.70

# Treatment

Successful treatment of mucormycosis relies on timely diagnosis, reversal of underlying predisposing factors, early surgical débridement of infected tissue, and rapid initiation of effective high-dose systemic antifungal therapy.187 Early diagnosis is critical to the outcome of mucormycosis because small focal lesions can be surgically resected before the lesions progress to involve critical structures or distal organs.50,121 Patients often have an indolent clinical presentation until extensive invasion or dissemination of the infection. Delays in the administration of systemic antifungal therapy increase the probability of patient death due to disseminated infection.106

Patients with suspected rhinocerebral mucormycosis should undergo a thorough examination and “staging” of their disease, including CT of the paranasal sinuses and lungs as well as endoscopic examination of nasal turbinates with biopsy of any suspicious lesions or necrotic eschars. Patient outcome can be improved if initial treatment decisions are based on frozen tissue samples from biopsy rather than waiting for tissues to be fixed and stained for histology.188 Rapid correction of predisposing conditions, such as control of hyperglycemia, reversal of ketoacidosis, and rapid tapering of glucocorticoid therapy, are critical for reversing conditions that favor fungal virulence and dissemination.**59** In rare cases, correction of diabetic ketoacidosis was sufficient to allow recovery from cavitary pulmonary mucormycosis without antifungal treatment.6 In neutropenic patients granulocyte transfusions may be beneficial as a temporary approach until granulocyte recovery.150

## Antifungal Therapy

No prospective randomized studies of the primary treatment of mucormycosis have been performed, owing to the rarity and heterogeneous nature of this mycosis. Most evidence concerning the activity of existing antifungals has come from retrospective small case series, case registries, prospective open-label studies, and animal models of infection. Because both surgical and medical interventions are simultaneously or sequentially performed, it is difficult to ascertain the relative efficacy of drug therapy alone.**17** Historically, the drug of choice for the treatment of mucormycosis was conventional amphotericin B deoxycholate (ABD), administered at the maximal tolerated doses of 1 to 1.5 mg/kg/day.189 Unfortunately, high doses of conventional amphotericin B are usually not tolerated for more than several days before renal function deteriorates, especially in patients with diabetes or receiving concomitant nephrotoxic therapies.

## Lipid Amphotericin B Formulations

Lipid formulations of amphotericin B are safer than ABD for long-term administration and, in our opinion, are the preferred first-line treatment for severe mucormycosis.187,190 Most experience in the treatment of mucormycosis has been with either liposomal amphotericin B (L-AMB) or amphotericin B lipid complex (ABLC). Although no comparative studies have been performed, outcomes with the use of the two lipid amphotericin B formulations are similar to those historically reported for conventional ABD, albeit with lower rates of nephrotoxicity.189

In one of the few published case series, 24 patients with mucormycosis and diabetes as the predominant underlying risk factors were treated with ABLC after failure or intolerance of the conventional ABD formulation.190,191 The overall response rate (improvement or cure of infection) was 71% (17/24 patients), with few reported toxic effects, even in patients with preexisting renal dysfunction. Several case series have reported the successful treatment of mucormycosis with the liposomal formulation of amphotericin B, sometimes administered at high doses (i.e., 10 mg/kg/day) for prolonged treatment courses.192,193

The optimal dosing approach for L-AMB in patients with mucormycosis is frequently debated. Preclinical pharmacokinetics/pharmacodynamics studies in murine models of pulmonary mucormycosis that simulated human dosing have suggested that ABLC at 5 mg/kg/day or L-AMB at 10 mg/kg/day results in rapid antifungal accumulation in the lung, reduced fungal burden, and improved survival.194 However, these animal models focus on short treatment periods and do not routinely assess nephrotoxicity of higher-dose L-AMB regimens. Both clinical and observational studies have suggested an early “window” of 10 to 14 days when nephrotoxicity risk is lowest with L-AMB, which may be shortened in patients receiving concomitant nephrotoxic agents or aggressive diuresis.**195**–197

In one of the few randomized trials that compared standard doses of L-AMB (3 mg/kg/day) to a higher dose-regimen (10 mg/kg/day for 14 days, then 3 mg/kg/day) for invasive aspergillosis, patients randomized to the higher-dosed L-AMB regimen failed to achieve higher response rates but experienced significantly higher rates of nephrotoxicity and severe hypokalemia.198

The feasibility of high-dose (10 mg/kg/day) L-AMB treatment for the initial treatment of mucormycosis was explored in a multicentric prospective French study of 40 patients with invasive mucormycosis.**199** The planned treatment of 10 mg/kg/day was administered as an infusion of at least 2 hours for 4 weeks. In patients in whom there was doubling of serum creatinine levels, compared with baseline, it was recommended that the L-AMB dose be reduced to 7.5 mg/kg/day. If creatinine values did not improve within 3 days, L-AMB dosing was further reduced to 5 mg/kg/day. Among the 33 patients who could be analyzed at 4 weeks after starting therapy or end of therapy, a favorable response was documented in 12 of 33 (36%) at week 4 and 14 of 31 (45%) by week 12. Most patients (24/31, 71%) underwent at least one surgical procedure. Of importance, although 4 weeks of high-dose L-AMB was planned, the average treatment duration at this dose was 13.5 days (range, 0–28), with 40% of patients experiencing a doubling in the baseline serum creatinine and severe hypokalemia (serum potassium <3 mmol/L). Therefore considerations for using doses of L-AMB higher than 5 mg/kg/day should take into account that a sizable proportion of patients will develop renal injury requiring dosage reduction or possibly a switch to triazole therapy after the first 1 to 2 weeks of therapy. Daily infusions of a liter of saline are used in some centers to reduce L-AMB nephrotoxicity in adults who can tolerate an increased sodium load.

## Triazoles

The prospects for using posaconazole in the treatment of mucormycosis has improved with the introduction of an extended-release tablet formulation with improved bioavailability compared with the older suspension, and an IV formulation solubilized in sulfobutyl ether β-cyclodextrin. These newer formulations are dosed differently than the oral suspension, which has to be administered two to four times daily in smaller doses to maximize absorption. The extended-release tablet and IV formulation of posaconazole are the preferred formulations of posaconazole for most patients due to their more reliable pharmacokinetics properties.**200**

Most of the published clinical experience concerning mucormycosis treatment with posaconazole has used the older suspension formulation administered at 800 mg/day in divided doses. In an open-label study evaluating posaconazole as salvage therapy (not initial therapy), the overall success rate of posaconazole (800 mg/day) was 70% in 24 patients, and it was well tolerated with only minimal GI side effects.201,202 Similarly, a retrospective survey of posaconazole-based salvage therapy in 91 patients with refractory mucormycosis indicated an overall success rate of 61%, including 65% in patients with pulmonary mucormycosis.203 Among patients who were not categorized as treatment successes, 21% had evidence of stable disease after 12 weeks of treatment. At present the US Food and Drug Administration (FDA) has not approved posaconazole for primary or salvage therapy of mucormycosis, indicating the need for further studies.

The extended-release tablet formulation of posaconazole is administered at a dose of 300 mg (three 100-mg delayed-release tablets) twice a day on the first day, then 300 mg daily. Although the absorption of the tablets is improved with food, the tablets have adequate bioavailability even in patients with poor dietary intake or receiving acid-suppression therapy, such as a proton pump inhibitor.204 The IV formulation of posaconazole is dosed at 300 mg IV twice daily on day 1, followed by 300 mg daily thereafter, and rapidly achieves plasma concentration exposures of greater than 500 ng/mL in 95% of patients, which often took more than a week in patients receiving posaconazole suspension.205 Although therapeutic drug monitoring has been recommended for posaconazole in *Aspergillus* treatment guidelines to ensure serum trough levels greater than 1.5 mg/L during the treatment of infection,**206**,207 a similar relationship between serum trough levels of posaconazole and outcome of mucormycosis has not been reported.

In 2015 the FDA approved isavuconazole for treatment of invasive mucormycosis based on an open observational report by the manufacturer**208** of 21 patients who received isavuconazole as primary therapy for proven or probable disease; 7 had the drug discontinued, 2 were still on therapy when reported, 6 died during isavuconazole treatment, and 6 were alive when isavuconazole treatment was considered completed. Results with salvage therapy in 16 patients were also considered favorable. The small numbers and diverse results make comparisons with amphotericin B and posaconazole difficult.**209** Isavuconazole may be a possible alternative to posaconazole or L-AMB, particularly for longer-term therapy. An advantage of isavuconazole is that it is administered as a prodrug formulation (isavuconazonium) in either an IV and oral formulation with excellent bioavailability that is not affected by dietary intake or acid-suppression therapy. Isavuconazole is dosed with a 372-mg loading dose administered every 8 hours for 6 doses (48 hours), then a 372-mg maintenance dose daily. Isavuconazole is generally well tolerated, making it a possible alternative for patients who are clinically stable and have limiting drug interactions with posaconazole or cannot tolerate the nephrotoxic effects of L-AMB. However, some species, such as *M. circinelloides,* exhibit MICs greater than achievable serum levels of patients with currently recommended isavuconazole dosing.**172** We have also observed cases of breakthrough mucormycosis during isavuconazole treatment in patients with prolonged neutropenia and relapsed hematologic malignancies.

## Combination Therapy

Successful treatment of mucormycosis with combinations of amphotericin B, terbinafine, rifampicin, L-AMB, posaconazole, and echinocandins has also been described in small case series and case reports.183,210 Interpretation of these studies is confounded by small numbers, retrospective nature, and confounding factors such as neutrophil recovery and surgery.210,211 One of the largest case-control studies evaluating the possible benefits of combination therapy for invasive mucormycosis was performed at MD Anderson Cancer Center,**212** which identified 47 patients who received early L-AMB monotherapy and 59 patients who received combination treatment. The most common combination regimens were L-AMB plus an echinocandin (46%), L-AMB plus posaconazole (27%), or triple combination therapy (27%). A propensity score analysis for combination therapy was used to attempt to adjust for confounding variables associated with prescription of combination therapy. The investigators could not identify any survival benefit for combination therapy over timely administration of L-AMB, even after propensity score adjustment (odds ratio, 0.8; 95% confidence interval, 0.3 to 2.4; *P* = .69) or if patients were stratified into groups for low versus high risk for mortality.**212**

## Treatment Duration

The duration of treatment required for mucormycosis is highly individualized to the patient. Near normalization of radiographic imaging, negative biopsy specimens, and cultures from the affected site and recovery from immunosuppression are indicators that a patient is a candidate for stopping antifungal therapy. Late relapses of mucormycosis after successful treatment have been reported several years after discontinuation of secondary posaconazole prophylaxis or onset of new immunosuppression.213 In one case relapsing disease was accompanied by increased 18F-fluorodeoxyglucose uptake in lesions detected by positron emission tomography–CT.213 Therefore continued follow-up of patients is critical in any patient who discontinues treatment for mucormycosis.

## Prophylaxis

Because mucormycosis is a relatively rare infection, primary prophylaxis is generally not recommended. Secondary prophylaxis is often desired in patients requiring further immunosuppression after treatment for mucormycosis. Posaconazole, and possibly isavuconazole, appears to be a safe option for patients who require continuous, oral long-term antifungal therapy because they remain at high risk for relapsing infection.213

## Surgical Management

In rhinosinusitis surgical débridement of infected tissue is a crucial component of therapy and should be urgently performed to limit the aggressive spread of infection to contiguous structures. Repeated removal of necrotic tissue or radical surgical resection (e.g., exenteration of the orbit) with subsequent reconstructive surgeries may be required for lifesaving control of rapidly evolving infection.118 However, rhinosinusitis has been treated successfully in select patients without radical resection, particularly when multimodality treatment options are used with careful follow-up.214 Extension to the brain usually portends a fatal outcome. Decisions regarding the extent of surgical débridement are highly individualized to the patient. Intraoperative frozen sections and MRI can help determine the extent of involved tissue and tissue margins. Conditions such as low platelet counts and other bleeding problems must be corrected with sufficient transfusions before surgical intervention. Unfortunately, bleeding risks may limit surgical options in some patients with profound thrombocytopenia.

In patients with pulmonary mucormycosis, surgical treatment in conjunction with systemic antifungal therapy has been shown to significantly improve survival compared with antifungal therapy alone.118,215 One large case series reported a mortality rate of 55% in patients who received systemic antifungal therapy alone compared with 27% in patients who received antifungal therapy plus surgical intervention.110 Although the reported outcomes may reflect a selection bias in offering surgery to less severely ill patients with unifocal disease, removal of infected or devitalized tissue early, when the infection is localized, provides the greatest benefit. Cavitation of lesions near the hilum has been followed by fatal hemoptysis, providing an incentive for resection in selected patients. Repeated surgeries are also necessary in some cases. The benefit of pulmonary resection of a dominant lung lesion (debulking) is unknown in patients with multifocal or disseminated mucormycosis.

## Adjunctive Therapies

Patients with profound neutropenia and progressive mucormycosis despite optimal therapy may be candidates for neutrophil transfusion. With currently available techniques, more than 1010 granulocytes can be infused, resulting in an immediate postinfusion absolute neutrophil count usually exceeding 1000/µL. Repeated infusions are needed every few days and can lead to diminishing response in the patient's neutrophil count due to allosensitization. Success of this bridging procedure in treating mucormycosis is still uncertain but likely depends ultimately on the patient's marrow recovery.

Several other adjunctive measures have been explored for improving tissue viability, impeding fungal proliferation, and improving host immunity. Hyperbaric oxygen therapy was reported to be a beneficial adjunct to standard surgical and antifungal therapy for mucormycosis, particularly for diabetic patients with rhinocerebral disease.216–218 Although this is not one of the approved uses of hyperbaric oxygen (see Chapter 50), the increased oxygen pressure achieved with hyperbaric oxygen may improve neutrophil activity and the putative oxidative killing effects of polyene antifungals.219 High oxygen concentrations have also been reported to inhibit growth of Mucorales in vitro and to improve the rate of wound healing by increasing the release of tissue growth factors.220 Lack of convincing clinical evidence supporting the benefit of hyperbaric oxygen therapy, however, limits its recommendation for routine clinical use for this expensive, controversial, and logistically difficult intervention for mucormycosis.71

Multiple immune-augmentation strategies have been proposed for mucormycosis, including administration of cytokines that enhance phagocytic activity, such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or IFN-γ alone or in combination with granulocyte transfusions. Various combinations of these approaches have been reported with some favorable outcomes in case reports.219,221 However, many of these immune-augmentation strategies carry some risk for enhancing inflammatory lung injury222,223; therefore the relative benefits of such adjunctive strategies must be balanced against the risk for increased harm to the patient.

## Prognosis

The site of infection and underlying host factors are the key prognostic determinants of mucormycosis outcome. Active hematologic malignancy, allogeneic HSCT, and disseminated infection are associated with poor outcome.166 In our experience, most patients with hematologic cancer who develop mucormycosis die within 12 weeks of diagnosis.121,**212**,224 However, earlier diagnosis of the disease and aggressive treatment have been associated with improved survival rates in recent series.166,**212** Correction of underlying immune impairment (e.g., rapid tapering of glucocorticoids), combined with aggressive multimodality treatment approaches, offer the best chance for patient survival.

# Entomophthoramycosis

Infections caused by fungi in the subphylum Entomophthoramycotina, called *entomophthoramycosis,* include both conidiobolomycosis and basidiobolomycosis. These are rare infections of the paranasal sinus and subcutaneous tissues, principally encountered in the tropics, that rarely affect other tissues.225 In contrast to mucormycosis, entomophthoramycosis is usually a chronic, nonangioinvasive infection in relatively immunocompetent individuals.226,227 Although rare, case clusters of invasive disease have been reported in both immunocompromised and immunocompetent patients.228,229 Conidiobolomycosis affects primarily the head and face, whereas basidiobolomycosis is often localized to the subcutaneous tissues of the trunk and arms or the GI tract.226,227 The infections are characterized by slow-growing, tumor-like masses in infected tissues that can remain indolent for years. Both fungi are common inhabitants of the soil throughout the world, including the United States. However, most cases of conidiobolomycosis are found in tropical Africa, South America, Central America, and Asia.226 Similarly, reports of cutaneous basidiobolomycosis are primarily concentrated in tropical areas of Africa and Southeast Asia and in the tropical and subtropical regions of Asia, Australia, and South America.227 Entomophthoramycosis also demonstrates some age specificity: conidiobolomycosis is uncommon in children, but 88% of basidiobolomycosis cases occur in patients younger than 20 years.230

## Conidiobolomycosis

Subcutaneous rhinofacial conidiobolomycosis is the most common manifestation of infection caused by *Conidiobolus coronatus.* Symptoms typically begin with nasal discharge, epistaxis, unilateral nasal obstruction, sinus tenderness, and extensive and persistent facial swelling that may result in disfiguration. The infection slowly progresses with granulomatous inflammation in the subcutaneous tissue without bone involvement or ulceration of the skin.231 Systemic symptoms are rare, but disseminated conidiobolomycosis has been observed.226 Infections with *Conidiobolus incongruus* are extremely rare but often more aggressive.159

## Basidiobolomycosis

Infections caused by *Basidiobolus ranarum* often begin as a nodular subcutaneous lesion on the trunk, arms, or buttocks. The mode of transmission for *B. ranarum* is assumed to be through minor trauma and insect bites. Fungal spores are found in the bristles of mites and are probably carried by other insects. *B. ranarum* has been theorized to be present on “toilet leaves” used for skin cleaning after a bowel movement, resulting in direct inoculation of the perineum.232 The predominance of lesions in the buttocks, thighs, and perineum would appear to support this theory. The subcutaneous lesions elicited by *B. ranarum* are typically firm but not painful, with edema around the involved sites. Deeper invasion of muscle underlying the subcutaneous tissue has been reported.227 Several cases have been reported of otherwise healthy persons with GI tract basidiobolomycosis, most often in the colon,233 that may present as obstruction or mimic the presentation of Crohn disease.232,234,235 Clinical features of GI basidiobolomycosis include abdominal pain, nausea, vomiting, diarrhea, or abdominal mass.235 Peripheral blood eosinophilia and high serum immunoglobulin E concentrations are usual. Most cases are slowly progressive locally and may be mistaken for Crohn disease or form large abdominal masses mimicking malignancy. Chronic fibrotic-appearing lesions, including angioinvasive disease reminiscent of mucormycosis seen in diabetic and immunocompromised patients, have also been described.229

## Diagnosis

In areas where entomophthoramycosis is common the diagnosis is often suspected from the clinical appearance of the patient and characteristic lesions or swelling.232,235 Definitive diagnosis requires biopsy of the involved site, with characteristic findings of broad, sparsely septated hyphae surrounded by eosinophilic granular material (Splendore-Hoeppli phenomena).232,236,237 Tissue eosinophilia and granulomatous inflammation are usual. Peripheral eosinophilia may also be present, but cultures from the infected site are often negative. PCR assay of DNA extracted from tissue or from the isolated fungus, followed by sequencing, may be the most useful confirmatory diagnostic test.13,233

## Differential Diagnosis

Eumycetomas have some clinical similarities to entomophthoramycosis, presenting as a chronic granulomatous fungal disease that affects the limbs, most commonly the feet (mycetoma pedis or Madura foot), and on occasion the abdomen, chest, and head, typically with draining sinuses. Eumycetomas can be differentiated by the presence of grains surrounded by neutrophils on biopsy and by culture. Pythiosis is usually a disease of horses, cattle, dogs, and cats but is a rare cause of subcutaneous disease in humans that can resemble entomophthoramycosis or can cause GI or disseminated infection resembling mucormycosis. Although the histologic appearance of the hyphae is similar, presence of vascular invasion and the appearance of motile zoospores on water culture of the causative organism, *Pythium insidiosum,* can distinguish the entities.13

## Therapy and Prevention

*Conidiobolus* spp. are generally more resistant to systemic antifungals than *Basidiobolus* spp.238 In the older literature agents used to treat entomophthoramycosis included potassium iodide, trimethoprim-sulfamethoxazole, ketoconazole, itraconazole, and amphotericin B with varying success and clinical outcome.226,227,239–**241** At present the preferred drugs for rhinofacial conidiobolomycosis appear to be a combination of a saturated solution of potassium iodide and itraconazole.**241** Surgical removal and reconstructive surgery for grossly swollen or disfigured tissues, combined with medical therapy, often provides the best chance for complete recovery. Subcutaneous basidiobolomycosis has been reported to respond to itraconazole.**242** Response of GI basidiobolomycosis to mold-active azoles has generally been favorable in small numbers of cases, including itraconazole, posaconazole, or voriconazole.**241**,**243**–245

# Key References

*The complete reference list is available online at Expert Consult.*

**7.** Sivagnanam S, Sengupta DJ, Hoogestraat D, et al. Seasonal clustering of sinopulmonary mucormycosis in patients with hematologic malignancies at a large comprehensive cancer center. Antimicrob Resist Infect Control. 2017;6:123.

**11.** Tribble DR, Rodriguez CJ, Weintrob AC, et al. Environmental factors related to fungal wound contamination after combat trauma in Afghanistan, 2009-2011. Emerg Infect Dis. 2015;21:1759–1769.

**16.** Chibucos MC, Soliman S, Gebremariam T, et al. An integrated genomic and transcriptomic survey of mucormycosis-causing fungi. Nat Commun. 2016;7:12218.

**17.** Farmakiotis D, Kontoyiannis DP. Mucormycoses. Infect Dis Clin North Am. 2016;30:143–163.

**21.** Pana ZD, Seidel D, Skiada A, et al. Invasive mucormycosis in children: an epidemiologic study in European and non-European countries based on two registries. BMC Infect Dis. 2016;16:667.

**22.** Davoudi S, Graviss LS, Kontoyiannis DP. Healthcare-associated outbreaks due to Mucorales and other uncommon fungi. Eur J Clin Invest. 2015;45:767–773.

**23.** Cheng VCC, Chen JHK, Wong SCY, et al. Hospital outbreak of pulmonary and cutaneous zygomycosis due to contaminated linen items from substandard laundry. Clin Infect Dis. 2016;62:714–721.

**41.** Kontoyiannis DP, Yang H, Song J, et al. Prevalence, clinical and economic burden of mucormycosis-related hospitalizations in the United States: a retrospective study. BMC Infect Dis. 2016;16:730.

**51.** Lamoth F, Chung SJ, Damonti L, et al. Changing epidemiology of invasive mold infections in patients receiving azole prophylaxis. Clin Infect Dis. 2017;64:1619–1621.

**55.** Ibrahim AS, Voelz K. The mucormycete-host interface. Curr Opin Microbiol. 2017;40:40–45.

**59.** Gebremariam T, Lin L, Liu M, et al. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. J Clin Invest. 2016;126:2280–2294.

**61.** Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis—the bitter and the sweet. PLoS Pathog. 2017;13:e1006408.

**104.** Lass-Florl C, Aigner M, Nachbaur D, et al. Diagnosing filamentous fungal infections in immunocompromised patients applying computed tomography-guided percutaneous lung biopsies: a 12-year experience. Infection. 2017;45:867–875.

**107.** Caillot D, Valot S, Lafon I, et al. Is it time to include CT “reverse halo sign” and qPCR targeting Mucorales in serum to EORTC-MSG criteria for the diagnosis of pulmonary mucormycosis in leukemia patients? Open Forum Infect Dis. 2016;3:ofw190.

**113.** Kontoyiannis DP, Lewis RE. Treatment principles for the management of mold infections. Cold Spring Harb Perspect Med. 2015;5:a019737.

**116.** Nam BD, Kim TJ, Lee KS, et al. Pulmonary mucormycosis: serial morphologic changes on computed tomography correlate with clinical and pathologic findings. Eur Radiol. 2018;28:788–795.

**125.** Rodriguez-Lobato E, Ramirez-Hobak L, Aquino-Matus JE, et al. Primary cutaneous mucormycosis caused by *Rhizopus oryzae:* a case report and review of literature. Mycopathologia. 2017;182:387–392.

**135.** Taj-Aldeen SJ, Gamaletsou MN, Rammaert B, et al. Bone and joint infections caused by Mucormycetes: a challenging osteoarticular mycosis of the twenty-first century. Med Mycol. 2017;55:691–704.

**162.** Normand AC, Cassagne C, Gautier M, et al. Decision criteria for MALDI-TOF MS-based identification of filamentous fungi using commercial and in-house reference databases. BMC Microbiol. 2017;17:25.

**163.** Cassagne C, Normand AC, L'Ollivier C, et al. Performance of MALDI-TOF MS platforms for fungal identification. Mycoses. 2016;59:678–690.

**167.** Springer J, Goldenberger D, Schmidt F, et al. Development and application of two independent real-time PCR assays to detect clinically relevant Mucorales species. J Med Microbiol. 2016;65:227–234.

**168.** Springer J, Lackner M, Ensinger C, et al. Clinical evaluation of a Mucorales-specific real-time PCR assay in tissue and serum samples. J Med Microbiol. 2016;65:1414–1421.

**172.** Arendrup MC, Jensen RH, Meletiadis J. In vitro activity of isavuconazole and comparators against clinical isolates of the Mucorales order. Antimicrob Agents Chemother. 2015;59:7735–7742.

**173.** Chowdhary A, Singh PK, Kathuria S, et al. Comparison of the EUCAST and CLSI broth microdilution methods for testing isavuconazole, posaconazole, and amphotericin B against molecularly identified Mucorales species. Antimicrob Agents Chemother. 2015;59:7882–7887.

**174.** Dannaoui E. Antifungal resistance in Mucorales. Int J Antimicrob Agents. 2017;50:617–621.

**176.** Espinel-Ingroff A, Alvarez-Fernandez M, Cantón E, et al. Multicenter study of epidemiological cutoff values and detection of resistance in *Candida* spp. to anidulafungin, caspofungin, and micafungin using the Sensititre YeastOne colorimetric method. Antimicrob Agents Chemother. 2015;59:6725–6732.

**177.** Lamoth F, Damonti L, Alexander BD. Role of antifungal susceptibility testing in non-*Aspergillus* invasive mold infections. J Clin Microbiol. 2016;54:1638–1640.

**185.** Gebremariam T, Alkhazraji S, Baldin C, et al. Prophylaxis with isavuconazole or posaconazole protect immunosuppressed mice from pulmonary mucormycosis. Antimicrob Agents Chemother. 2017;61:e02589-16.

**186.** Gebremariam T, Wiederhold NP, Alqarihi A, et al. Monotherapy or combination therapy of isavuconazole and micafungin for treating murine mucormycosis. J Antimicrob Chemother. 2017;72:462–466.

**195.** Stanzani M, Vianelli N, Cavo M, et al. Liposomal amphotericin B nephrotoxicity in patients with hematological malignancies: a retrospective cohort analysis. Antimicrob Agents Chemother. 2017;61:e02651-16.

**199.** Lanternier F, Poiree S, Elie C, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015;70:3116–3123.

**200.** Dekkers BGJ, Bakker M, van der Elst KCM, et al. Therapeutic drug monitoring of posaconazole: an update. Curr Fungal Infect Rep. 2016;10:51–61.

**206.** Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1–e60.

**208.** Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16:828–837.

**209.** Spellberg B, Brass E. The VITAL study: case control studies are hypothesis-generating. Lancet Infect Dis. 2016;16:886.

**212.** Kyvernitakis A, Torres HA, Jiang Y, et al. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. Clin Microbiol Infect. 2016;22:811.e811–811.e818.

**241.** Gupta M, Narang T, Kaur RJ, et al. A prospective case series evaluating efficacy and safety of combination of itraconazole and potassium iodide in rhinofacial conidiobolomycosis. Int J Dermatol. 2016;55:208–214.

**242.** Kumaravel S, Bharath K, Rajesh NG, et al. Delay and misdiagnosis of basidiobolomycosis in tropical South India: case series and review of the literature. Paediatr Int Child Health. 2016;36:52–57.

**243.** Mandhan P, Hassan KO, Samaan SM, et al. Visceral basidiobolomycosis: an overlooked infection in immunocompetent children. Afr J Paediatr Surg. 2015;12:193–196.

# References

1. Paltauf A. Mycosis mucorina: ein Beitrag zur Kenntnis der menschlichen Fadenpiltzer-krankungen. Virchows Arch Pathol Anat. 1885;102:543–564.

2. Kwon-Chung KJ. Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. Clin Infect Dis. 2012;54 Suppl 1:S8–S15.

3. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634–653.

4. Skiada A, Pagano L, Groll A, et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis. Clin Microbiol Infect. 2011;17:1859–1867.

5. Petrikkos G, Skiada A, Drogari-Apiranthitou M. Epidemiology of mucormycosis in Europe. Clin Microbiol Infect. 2014;20 Suppl 6:67–73.

6. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev. 2000;13:236–301.

**7.** Sivagnanam S, Sengupta DJ, Hoogestraat D, et al. Seasonal clustering of sinopulmonary mucormycosis in patients with hematologic malignancies at a large comprehensive cancer center. Antimicrob Resist Infect Control. 2017;6:123.

8. Shpitzer T, Keller N, Wolf M, et al. Seasonal variations in rhino-cerebral *Mucor* infection. Ann Otol Rhinol Laryngol. 2005;114:695–698.

9. Neblett Fanfair R, Benedict K, Bos J, et al. Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011. N Engl J Med. 2012;367:2214–2225.

10. Andresen D, Donaldson A, Choo L, et al. Multifocal cutaneous mucormycosis complicating polymicrobial wound infections in a tsunami survivor from Sri Lanka. Lancet. 2005;365:876–878.

**11.** Tribble DR, Rodriguez CJ, Weintrob AC, et al. Environmental factors related to fungal wound contamination after combat trauma in Afghanistan, 2009-2011. Emerg Infect Dis. 2015;21:1759–1769.

12. Ma L-J, Ibrahim AS, Skory C, et al. Genomic analysis of the basal lineage fungus *Rhizopus oryzae* reveals a whole-genome duplication. PLoS Genet. 2009;5:e1000549.

13. Mendoza L, Vilela R, Voelz K, et al. Human fungal pathogens of Mucorales and Entomophthorales. Cold Spring Harb Perspect Med. 2014;5.

14. Vitale RG, de Hoog GS, Schwarz P, et al. Antifungal susceptibility and phylogeny of opportunistic members of the order Mucorales. J Clin Microbiol. 2012;50:66–75.

15. Lewis RE, Lortholary O, Spellberg B, et al. How does antifungal pharmacology differ for mucormycosis versus aspergillosis? Clin Infect Dis. 2012;54 Suppl 1(suppl 1):S67–S72.

**16.** Chibucos MC, Soliman S, Gebremariam T, et al. An integrated genomic and transcriptomic survey of mucormycosis-causing fungi. Nat Commun. 2016;7:12218.

**17.** Farmakiotis D, Kontoyiannis DP. Mucormycoses. Infect Dis Clin North Am. 2016;30:143–163.

18. Dioverti MV, Cawcutt KA, Abidi M, et al. Gastrointestinal mucormycosis in immunocompromised hosts. Mycoses. 2015;58:714–718.

19. Spellberg B. Gastrointestinal mucormycosis: an evolving disease. Gastroenterol Hepatol (N Y). 2012;8:140–142.

20. Lee SC, Billmyre RB, Li A, et al. Analysis of a food-borne fungal pathogen outbreak: virulence and genome of a *Mucor circinelloides* isolate from yogurt. MBio. 2014;5:e01390-01314.

**21.** Pana ZD, Seidel D, Skiada A, et al. Invasive mucormycosis in children: an epidemiologic study in European and non-European countries based on two registries. BMC Infect Dis. 2016;16:667.

**22.** Davoudi S, Graviss LS, Kontoyiannis DP. Healthcare-associated outbreaks due to Mucorales and other uncommon fungi. Eur J Clin Invest. 2015;45:767–773.

**23.** Cheng VCC, Chen JHK, Wong SCY, et al. Hospital outbreak of pulmonary and cutaneous zygomycosis due to contaminated linen items from substandard laundry. Clin Infect Dis. 2016;62:714–721.

24. Gartenberg G, Bottone EJ, Keusch GT, et al. Hospital-acquired mucormycosis *(Rhizopus rhizopodiformis)* of skin and subcutaneous tissue: epidemiology, mycology and treatment. N Engl J Med. 1978;299:1115–1118.

25. Mead JH, Lupton GP, Dillavou CL, et al. Cutaneous *Rhizopus* infection. Occurrence as a postoperative complication associated with an elasticized adhesive dressing. JAMA. 1979;242:272–274.

26. Chakrabarti A, Kumar P, Padhye AA, et al. Primary cutaneous zygomycosis due to *Saksenaea vasiformis* and *Apophysomyces elegans*. Clin Infect Dis. 1997;24:580–583.

27. Jain JK, Markowitz A, Khilanani PV, et al. Localized mucormycosis following intramuscular corticosteroid. Case report and review of the literature. Am J Med Sci. 1978;275:209–216.

28. Verweij PE, Voss A, Donnelly JP, et al. Wooden sticks as the source of a pseudoepidemic of infection with *Rhizopus microsporus* var. rhizopodiformis among immunocompromised patients. J Clin Microbiol. 1997;35:2422–2423.

29. Paydas S, Yavuz S, Disel U, et al. Mucormycosis of the tongue in a patient with acute lymphoblastic leukemia: a possible relation with use of a tongue depressor. Am J Med. 2003;114:618–620.

30. Duffy J, Harris J, Gade L, et al. Mucormycosis outbreak associated with hospital linens. Pediatr Infect Dis J. 2014;33:472–476.

31. Baker RD. Mucormycosis; a new disease? J Am Med Assoc. 1957;163:805–808.

32. Baker RD. Pulmonary mucormycosis. Am J Pathol. 1956;32:287–313.

33. Artis WM, Fountain JA, Delcher HK, et al. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. Diabetes. 1982;31:1109–1114.

34. Boelaert JR, de Locht M, Van Cutsem J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. J Clin Invest. 1993;91:1979–1986.

35. Boelaert JR, van Roost GF, Vergauwe PL, et al. The role of desferrioxamine in dialysis-associated mucormycosis: report of three cases and review of the literature. Clin Nephrol. 1988;29:261–266.

36. Boelaert JR, Vergauwe PL, Vandepitte JM. Mucormycosis infection in dialysis patients. Ann Intern Med. 1987;107:782–783.

37. Sims CR, Ostrosky-Zeichner L. Contemporary treatment and outcomes of zygomycosis in a non-oncologic tertiary care center. Arch Med Res. 2007;38:90–93.

38. Hospenthal DR, Chung KK, Lairet K, et al. *Saksenaea erythrospora* infection following combat trauma. J Clin Microbiol. 2011;49:3707–3709.

39. Fahimzad A, Chavoshzadeh Z, Abdollahpour H, et al. Necrosis of nasal cartilage due to mucormycosis in a patient with severe congenital neutropenia due to HAX1 deficiency. J Investig Allergol Clin Immunol. 2008;18:469–472.

40. Kumar N, Hanks ME, Chandrasekaran P, et al. Gain-of-function signal transducer and activator of transcription 1 (STAT1) mutation-related primary immunodeficiency is associated with disseminated mucormycosis. J Allergy Clin Immunol. 2014;134:236–239.

**41.** Kontoyiannis DP, Yang H, Song J, et al. Prevalence, clinical and economic burden of mucormycosis-related hospitalizations in the United States: a retrospective study. BMC Infect Dis. 2016;16:730.

42. Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54(suppl 1):S23–S34.

43. Lanternier F, Dannaoui E, Morizot G, et al. A global analysis of mucormycosis in France: the RetroZygo Study (2005-2007). Clin Infect Dis. 2012;54 Suppl 1:S35–S43.

44. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010;50:1091–1100.

45. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50:1101–1111.

46. Kontoyiannis DP, Azie N, Franks B, et al. Prospective antifungal therapy (PATH) alliance: focus on mucormycosis. Mycoses. 2014;57:240–246.

47. Parker VJ, Jergens AE, Whitley EM, et al. Isolation of *Cokeromyces recurvatus* from the gastrointestinal tract in a dog with protein-losing enteropathy. J Vet Diagn Invest. 2011;23:1014–1016.

48. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010;50:1091–1100.

49. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med. 2004;350:950–952.

50. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005;191:1350–1360.

**51.** Lamoth F, Chung SJ, Damonti L, et al. Changing epidemiology of invasive mold infections in patients receiving azole prophylaxis. Clin Infect Dis. 2017;64:1619–1621.

52. England AC 3rd, Weinstein M, Ellner JJ, et al. Two cases of rhinocerebral zygomycosis (mucormycosis) with common epidemiologic and environmental features. Am Rev Respir Dis. 1981;124:497–498.

53. Lueg EA, Ballagh RH, Forte V. Analysis of the recent cluster of invasive fungal sinusitis at the Toronto Hospital for Sick Children. J Otolaryngol. 1996;25:366–370.

54. Prevoo RL, Starink TM, de Haan P. Primary cutaneous mucormycosis in a healthy young girl. Report of a case caused by *Mucor hiemalis Wehmer*. J Am Acad Dermatol. 1991;24(5 Pt 2):882–885.

**55.** Ibrahim AS, Voelz K. The mucormycete-host interface. Curr Opin Microbiol. 2017;40:40–45.

56. Bouchara JP, Oumeziane NA, Lissitzky JC, et al. Attachment of spores of the human pathogenic fungus *Rhizopus oryzae* to extracellular matrix components. Eur J Cell Biol. 1996;70:76–83.

57. Ibrahim AS, Spellberg B, Avanessian V, et al. *Rhizopus oryzae* adheres to, is phagocytosed by, and damages endothelial cells in vitro. Infect Immun. 2005;73:778–783.

58. Liu M, Spellberg B, Phan QT, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest. 2010;120:1914–1924.

**59.** Gebremariam T, Lin L, Liu M, et al. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. J Clin Invest. 2016;126:2280–2294.

60. Gebremariam T, Liu M, Luo G, et al. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest. 2014;124:237–250.

**61.** Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis—the bitter and the sweet. PLoS Pathog. 2017;13:e1006408.

62. de Locht M, Boelaert JR, Schneider YJ. Iron uptake from ferrioxamine and from ferrirhizoferrin by germinating spores of *Rhizopus microsporus*. Biochem Pharmacol. 1994;47:1843–1850.

63. Ibrahim AS, Gebremariam T, Lin L, et al. The high affinity iron permease is a key virulence factor required for *Rhizopus oryzae* pathogenesis. Mol Microbiol. 2010;77:587–604.

64. Alexander J, Limaye AP, Ko CW, et al. Association of hepatic iron overload with invasive fungal infection in liver transplant recipients. Liver Transpl. 2006;12:1799–1804.

65. Artis WM, Patrusky E, Rastinejad F, et al. Fungistatic mechanism of human transferrin for *Rhizopus oryzae* and *Trichophyton mentagrophytes:* alternative to simple iron deprivation. Infect Immun. 1983;41:1269–1278.

66. Boelaert JR, Van Cutsem J, de Locht M, et al. Deferoxamine augments growth and pathogenicity of *Rhizopus,* while hydroxypyridinone chelators have no effect. Kidney Int. 1994;45:667–671.

67. Boelaert JR, de Locht M, Schneider YJ. The effect of deferoxamine on different zygomycetes. J Infect Dis. 1994;169:231–232.

68. Ibrahim AS, Gebermariam T, Fu Y, et al. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J Clin Invest. 2007;117:2649–2657.

69. Reed C, Ibrahim A, Edwards JE Jr, et al. Deferasirox, an iron-chelating agent, as salvage therapy for rhinocerebral mucormycosis. Antimicrob Agents Chemother. 2006;50:3968–3969.

70. Spellberg B, Ibrahim AS, Chin-Hong PV, et al. The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. J Antimicrob Chemother. 2012;67:715–722.

71. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect. 2014;20 Suppl 3:5–26.

72. Waldorf AR, Levitz SM, Diamond RD. In vivo bronchoalveolar macrophage defense against *Rhizopus oryzae* and *Aspergillus fumigatus*. J Infect Dis. 1984;150:752–760.

73. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against *Rhizopus*. J Clin Invest. 1984;74:150–160.

74. Schmidt S, Tramsen L, Perkhofer S, et al. *Rhizopus oryzae* hyphae are damaged by human natural killer (NK) cells, but suppress NK cell mediated immunity. Immunobiology. 2013;218:939–944.

75. Chamilos G, Lewis RE, Lamaris G, et al. Zygomycetes hyphae trigger an early, robust proinflammatory response in human polymorphonuclear neutrophils through Toll-like receptor 2 induction but display relative resistance to oxidative damage. Antimicrob Agents Chemother. 2008;52:722–724.

76. Diamond RD, Haudenschild CC, Erickson NF 3rd. Monocyte-mediated damage to *Rhizopus oryzae* hyphae in vitro. Infect Immun. 1982;38:292–297.

77. Perkhofer S, Kainzner B, Kehrel BE, et al. Potential antifungal effects of human platelets against Zygomycetes in vitro. J Infect Dis. 2009;200:1176–1179.

78. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet. 2003;362:1828–1838.

79. Chinn RY, Diamond RD. Generation of chemotactic factors by *Rhizopus oryzae* in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. Infect Immun. 1982;38:1123–1129.

80. Potenza L, Vallerini D, Barozzi P, et al. Mucorales-specific T cells emerge in the course of invasive mucormycosis and may be used as a surrogate diagnostic marker in high-risk patients. Blood. 2011;118:5416–5419.

81. Chamilos G, Ganguly D, Lande R, et al. Generation of IL-23 producing dendritic cells (DCs) by airborne fungi regulates fungal pathogenicity via the induction of T(H)-17 responses. PLoS ONE. 2010;5:e12955.

82. Guo D, Jaber BL, Lee S, et al. Impact of iron dextran on polymorphonuclear cell function among hemodialysis patients. Clin Nephrol. 2002;58:134–142.

83. Omara FO, Blakley BR. The effects of iron deficiency and iron overload on cell-mediated immunity in the mouse. Br J Nutr. 1994;72:899–909.

84. Omara FO, Blakley BR, Huang HS. Effect of iron status on endotoxin-induced mortality, phagocytosis and interleukin-1 alpha and tumor necrosis factor-alpha production. Vet Hum Toxicol. 1994;36:423–428.

85. Cantinieaux B, Janssens A, Boelaert JR, et al. Ferritin-associated iron induces neutrophil dysfunction in hemosiderosis. J Lab Clin Med. 1999;133:353–361.

86. Sheldon WH, Bauer H. Activation of quiescent mucormycotic granulomata in rabbits by induction of acute alloxan diabetes. J Exp Med. 1958;108:171–178.

87. Chandler FW, Kaplan W, Ajello L A colour atlas and textbook of the histopathology of mycotic diseases; 1980.

88. Ben-Ami R, Luna M, Lewis RE, et al. A clinicopathological study of pulmonary mucormycosis in cancer patients: extensive angioinvasion but limited inflammatory response. J Infect. 2009;59:134–138.

89. Stergiopoulou T, Meletiadis J, Roilides E, et al. Host-dependent patterns of tissue injury in invasive pulmonary aspergillosis. Am J Clin Pathol. 2007;127:349–355.

90. Mallis A, Mastronikolis SN, Naxakis SS. Papadas AT. Rhinocerebral mucormycosis: an update. Eur Rev Med Pharmacol Sci. 2010;14:987–992.

91. Yohai RA, Bullock JD, Aziz AA, et al. Survival factors in rhino-orbital-cerebral mucormycosis. Surv Ophthalmol. 1994;39:3–22.

92. Ochiai H, Iseda T, Miyahara S, et al. Rhinocerebral mucormycosis–case report. Neurol Med Chir (Tokyo). 1993;33:373–376.

93. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. Arch Pathol Lab Med. 2001;125:375–378.

94. Ferguson BJ. Is your case report really an invasive fungal rhinosinusitis? Laryngoscope. 2005;115:560, author reply 560–562.

95. Demirag A, Elkhammas EA, Henry ML, et al. Pulmonary *Rhizopus* infection in a diabetic renal transplant recipient. Clin Transplant. 2000;14:8–10.

96. Tsai TC, Hou CC, Chou MS, et al. Rhinosino-orbital mucormycosis causing cavernous sinus thrombosis and internal carotid artery occlusion: radiological findings in a patient with treatment failure. Kaohsiung J Med Sci. 1999;15:556–561.

97. Sehgal A, Raghavendran M, Kumar D, et al. Rhinocerebral mucormycosis causing basilar artery aneurysm with concomitant fungal colonic perforation in renal allograft recipient: a case report. Transplantation. 2004;78:949–950.

98. Delbrouck C, Jacobs F, Fernandez Aguilar S, et al. Carotid artery occlusion due to fulminant rhinocerebral mucormycosis. Acta Otorhinolaryngol Belg. 2004;58:135–140.

99. Howells RC, Ramadan HH. Usefulness of computed tomography and magnetic resonance in fulminant invasive fungal rhinosinusitis. Am J Rhinol. 2001;15:255–261.

100. Fatterpekar G, Mukherji S, Arbealez A, et al. Fungal diseases of the paranasal sinuses. Semin Ultrasound CT MR. 1999;20:391–401.

101. Greenberg MR, Lippman SM, Grinnell VS, et al. Computed tomographic findings in orbital Mucor. West J Med. 1985;143:102–103.

102. Greenberg RN, Scott LJ, Vaughn HH, et al. Zygomycosis (mucormycosis): emerging clinical importance and new treatments. Curr Opin Infect Dis. 2004;17:517–525.

103. Chamilos G, Marom EM, Lewis RE, et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis. 2005;41:60–66.

**104.** Lass-Florl C, Aigner M, Nachbaur D, et al. Diagnosing filamentous fungal infections in immunocompromised patients applying computed tomography-guided percutaneous lung biopsies: a 12-year experience. Infection. 2017;45:867–875.

105. Lass-Florl C, Resch G, Nachbaur D, et al. The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. Clin Infect Dis. 2007;45:e101–e104.

106. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying Amphotericin B–based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis. 2008;47:503–509.

**107.** Caillot D, Valot S, Lafon I, et al. Is it time to include CT “reverse halo sign” and qPCR targeting Mucorales in serum to EORTC-MSG criteria for the diagnosis of pulmonary mucormycosis in leukemia patients? Open Forum Infect Dis. 2016;3:ofw190.

108. Legouge C, Caillot D, Chretien ML, et al. The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia? Clin Infect Dis. 2014;58:672–678.

109. Gupta N, Kumar R, Prasad R. Reversed halo sign. Indian J Chest Dis Allied Sci. 2014;56:247–248.

109a. Thomas R, Madan R, Gooptu M, et al. Significance of the reverse halo sign in immunocompromised patients. AJR Am J Roentgenol. 2019;30:1–6.

110. Lee FY, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. Arch Intern Med. 1999;159:1301–1309.

111. Gupta KL, Khullar DK, Behera D, et al. Pulmonary mucormycosis presenting as fatal massive haemoptysis in a renal transplant recipient. Nephrol Dial Transplant. 1998;13:3258–3260.

112. Funada H, Matsuda T. Pulmonary mucormycosis in a hematology ward. Intern Med. 1996;35:540–544.

**113.** Kontoyiannis DP, Lewis RE. Treatment principles for the management of mold infections. Cold Spring Harb Perspect Med. 2015;5:a019737.

114. Lanternier F, Sun H-Y, Ribaud P, et al. Mucormycosis in organ and stem cell transplant recipients. Clin Infect Dis. 2012;54:1629–1636.

115. Trifilio SM, Bennett CL, Yarnold PR, et al. Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. Bone Marrow Transplant. 2007;39:425–429.

**116.** Nam BD, Kim TJ, Lee KS, et al. Pulmonary mucormycosis: serial morphologic changes on computed tomography correlate with clinical and pathologic findings. Eur Radiol. 2018;28:788–795.

117. McAdams HP, Rosado de Christenson M, Strollo DC, et al. Pulmonary mucormycosis: radiologic findings in 32 cases. AJR Am J Roentgenol. 1997;168:1541–1548.

118. Tedder M, Spratt JA, Anstadt MP, et al. Pulmonary mucormycosis: results of medical and surgical therapy. Ann Thorac Surg. 1994;57:1044–1050.

119. Wahba H, Truong MT, Lei X, et al. Reversed halo sign in invasive pulmonary fungal infections. Clin Infect Dis. 2008;46:1733–1737.

120. Georgiadou SP, Sipsas NV, Marom EM, et al. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis. 2011;52:1144–1155.

121. Kontoyiannis DP, Wessel VC, Bodey GP, et al. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis. 2000;30:851–856.

122. O'Connell MA, Pluss JL, Schkade P, et al. *Rhizopus*-induced hypersensitivity pneumonitis in a tractor driver. J Allergy Clin Immunol. 1995;95:779–780.

123. Hedenstierna G, Alexandersson R, Belin L, et al. Lung function and *Rhizopus* antibodies in wood trimmers. A cross-sectional and longitudinal study. Int Arch Occup Environ Health. 1986;58:167–177.

124. Bearer EA, Nelson PR, Chowers MY, et al. Cutaneous zygomycosis caused by *Saksenaea vasiformis* in a diabetic patient. J Clin Microbiol. 1994;32:1823–1824.

**125.** Rodriguez-Lobato E, Ramirez-Hobak L, Aquino-Matus JE, et al. Primary cutaneous mucormycosis caused by *Rhizopus oryzae:* a case report and review of literature. Mycopathologia. 2017;182:387–392.

126. De Decker K, Van Poucke S, Wojciechowski M, et al. Successful use of posaconazole in a pediatric case of fungal necrotizing fasciitis. Pediatr Crit Care Med. 2006;7:482–485.

127. Devi SC, Kanungo R, Barreto E, et al. Favorable outcome of amphotericin B treatment of zygomycotic necrotizing fascitis caused by *Apophysomyces elegans*. Int J Dermatol. 2008;47:407–409.

128. Jain D, Kumar Y, Vasishta RK, et al. Zygomycotic necrotizing fasciitis in immunocompetent patients: a series of 18 cases. Mod Pathol. 2006;19:1221–1226.

129. Kordy FN, Al-Mohsen IZ, Hashem F, et al. Successful treatment of a child with posttraumatic necrotizing fasciitis caused by *Apophysomyces elegans:* case report and review of literature. Pediatr Infect Dis J. 2004;23:877–879.

130. Lakshmi V, Rani TS, Sharma S, et al. Zygomycotic necrotizing fasciitis caused by *Apophysomyces elegans*. J Clin Microbiol. 1993;31:1368–1369.

131. Thami GP, Kaur S, Bawa AS, et al. Post-surgical zygomycotic necrotizing subcutaneous infection caused by *Absidia corymbifera*. Clin Exp Dermatol. 2003;28:251–253.

132. Nouri-Majalan N, Moghimi M. Skin mucormycosis presenting as an erythema-nodosum-like rash in a renal transplant recipient: a case report. J Med Case Rep. 2008;2:112.

133. Vernon SE, Dave SP. Cutaneous zygomycosis associated with urate panniculitis. Am J Dermatopathol. 2006;28:327–330.

134. Farmakiotis D, Ciurea AM, Cahuayme-Zuniga L, et al. The diagnostic yield of skin biopsy in patients with leukemia and suspected infection. J Infect. 2013;67:265–272.

**135.** Taj-Aldeen SJ, Gamaletsou MN, Rammaert B, et al. Bone and joint infections caused by Mucormycetes: a challenging osteoarticular mycosis of the twenty-first century. Med Mycol. 2017;55:691–704.

136. Bittencourt AL, Ayala MA, Ramos EA. A new form of abdominal zygomycosis different from mucormycosis: report of two cases and review of the literature. Am J Trop Med Hyg. 1979;28:564–569.

137. Park YS, Lee JD, Kim TH, et al. Gastric mucormycosis. Gastrointest Endosc. 2002;56:904–905.

138. Oliver MR, Van Voorhis WC, Boeckh M, et al. Hepatic mucormycosis in a bone marrow transplant recipient who ingested naturopathic medicine. Clin Infect Dis. 1996;22:521–524.

139. Joshita S, Kitano K, Nagaya T, et al. Zygomycosis presenting as acute myocardial infarction during hematological malignancies. Intern Med. 2008;47:839–842.

140. Naumann R, Kerkmann ML, Schuler U, et al. *Cunninghamella bertholletiae* infection mimicking myocardial infarction. Clin Infect Dis. 1999;29:1580–1581.

141. Benbow EW, Bonshek RE, Stoddart RW. Endobronchial zygomycosis. Thorax. 1987;42:553–554.

142. Polo JR, Luno J, Menarguez C, et al. Peritoneal mucormycosis in a patient receiving continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1989;13:237–239.

143. Nakamura M, Weil WB Jr, Kaufman DB. Fatal fungal peritonitis in an adolescent on continuous ambulatory peritoneal dialysis: association with deferoxamine. Pediatr Nephrol. 1989;3:80–82.

144. Branton MH, Johnson SC, Brooke JD, et al. Peritonitis due to *Rhizopus* in a patient undergoing continuous ambulatory peritoneal dialysis. Rev Infect Dis. 1991;13:19–21.

145. Schwartz JR, Nagle MG, Elkins RC, et al. Mucormycosis of the trachea: an unusual cause of acute upper airway obstruction. Chest. 1982;81:653–654.

146. Connor BA, Anderson RJ, Smith JW. Mucor mediastinitis. Chest. 1979;75:525–526.

147. Echols RM, Selinger DS, Hallowell C, et al. *Rhizopus* osteomyelitis. A case report and review. Am J Med. 1979;66:141–145.

148. Mishra B, Mandal A, Kumar N. Mycotic prosthetic-valve endocarditis. J Hosp Infect. 1992;20:122–125.

149. Roy TM, Anderson KC, Farrow JR. Cardiac mucormycosis complicating diabetes mellitus. J Diabet Complications. 1990;4:132–135.

150. Lussier N, Laverdiere M, Weiss K, et al. Primary renal mucormycosis. Urology. 1998;52:900–903.

1. Tierney MR, Baker AS. Infections of the head and neck in diabetes mellitus. Infect Dis Clin North Am. 1995;9:195–216.
2. Bosken CH, Szporn AH, Kleinerman J. Superior vena cava syndrome due to mucormycosis in a patient with lymphoma. Mt Sinai J Med. 1987;54:508–511.
3. Air EL, Vagal AA, Kendler A, et al. Isolated cerebellar mucormycosis, slowly progressive over 1 year in an immunocompetent patient. Surg Neurol Int. 2010;1:81.
4. Verma A, Brozman B, Petito CK. Isolated cerebral mucormycosis: report of a case and review of the literature. J Neurol Sci. 2006;240:65–69.
5. Cuadrado LM. Cerebral mucormycosis associated with intravenous drug use. Clin Infect Dis. 1996;22:198.
6. Hopkins RJ, Rothman M, Fiore A, et al. Cerebral mucormycosis associated with intravenous drug use: three case reports and review. Clin Infect Dis. 1994;19:1133–1137.
7. Leen CL, Brettle RP. Fungal infections in drug users. J Antimicrob Chemother. 1991;28 Suppl A:83–96.
8. Glazer M, Nusair S, Breuer R, et al. The role of BAL in the diagnosis of pulmonary mucormycosis. Chest. 2000;117:279–282.
9. Chayakulkeeree M, Ghannoum MA, Perfect JR. Zygomycosis: the re-emerging fungal infection. Eur J Clin Microbiol Infect Dis. 2006;25:215–229.
10. Ruchel R, Schaffrinski M, Seshan KR, et al. Vital staining of fungal elements in deep-seated mycotic lesions during experimental murine mycoses using the parenterally applied optical brightener Blankophor. Med Mycol. 2000;38:231–237.
11. Hammond SP, Bialek R, Milner DA, et al. Molecular methods to improve diagnosis and identification of mucormycosis. J Clin Microbiol. 2011;49:2151–2153.
12. Normand AC, Cassagne C, Gautier M, et al. Decision criteria for MALDI-TOF MS-based identification of filamentous fungi using commercial and in-house reference databases. BMC Microbiol. 2017;17:25.
13. Cassagne C, Normand AC, L'Ollivier C, et al. Performance of MALDI-TOF MS platforms for fungal identification. Mycoses. 2016;59:678–690.
14. Kontoyiannis DP, Chamilos G, Hassan SA, et al. Increased culture recovery of Zygomycetes under physiologic temperature conditions. Am J Clin Pathol. 2007;127:208–212.
15. Tarrand JJ, Lichterfeld M, Warraich I, et al. Diagnosis of invasive septate mold infections. A correlation of microbiological culture and histologic or cytologic examination. Am J Clin Pathol. 2003;119:854–858.
16. Hammond SP, Baden LR, Marty FM. Mortality in hematologic malignancy and hematopoietic stem cell transplant patients with mucormycosis, 2001 to 2009. Antimicrob Agents Chemother. 2011;55:5018–5021.
17. Springer J, Goldenberger D, Schmidt F, et al. Development and application of two independent real-time PCR assays to detect clinically relevant Mucorales species. J Med Microbiol. 2016;65:227–234.
18. Springer J, Lackner M, Ensinger C, et al. Clinical evaluation of a Mucorales-specific real-time PCR assay in tissue and serum samples. J Med Microbiol. 2016;65:1414–1421.
19. Kobayashi M, Togitani K, Machida H, et al. Molecular polymerase chain reaction diagnosis of pulmonary mucormycosis caused by *Cunninghamella bertholletiae*. Respirology. 2004;9:397–401.
20. Bialek R, Konrad F, Kern J, et al. PCR based identification and discrimination of agents of mucormycosis and aspergillosis in paraffin wax embedded tissue. J Clin Pathol. 2005;58:1180–1184.
21. Rickerts V, Atta J, Herrmann S, et al. Successful treatment of disseminated mucormycosis with a combination of liposomal amphotericin B and posaconazole in a patient with acute myeloid leukaemia. Mycoses. 2006;49 Suppl 1:27–30.
22. Arendrup MC, Jensen RH, Meletiadis J. In vitro activity of isavuconazole and comparators against clinical isolates of the Mucorales order. Antimicrob Agents Chemother. 2015;59:7735–7742.
23. Chowdhary A, Singh PK, Kathuria S, et al. Comparison of the EUCAST and CLSI broth microdilution methods for testing isavuconazole, posaconazole, and amphotericin B against molecularly identified Mucorales species. Antimicrob Agents Chemother. 2015;59:7882–7887.
24. Dannaoui E. Antifungal resistance in Mucorales. Int J Antimicrob Agents. 2017;50:617–621.
25. Espinel-Ingroff A, Bartlett M, Chaturvedi V, et al. Optimal susceptibility testing conditions for detection of azole resistance in *Aspergillus* spp.: NCCLS collaborative evaluation. National Committee for Clinical Laboratory Standards. Antimicrob Agents Chemother. 2001;45:1828–1835.
26. Espinel-Ingroff A, Alvarez-Fernandez M, Cantón E, et al. Multicenter study of epidemiological cutoff values and detection of resistance in *Candida* spp. to anidulafungin, caspofungin, and micafungin using the Sensititre YeastOne colorimetric method. Antimicrob Agents Chemother. 2015;59:6725–6732.
27. Lamoth F, Damonti L, Alexander BD. Role of antifungal susceptibility testing in non-*Aspergillus* invasive mold infections. J Clin Microbiol. 2016;54:1638–1640.
28. Dannaoui E, Rijs AJ, Verweij PE. Invasive infections due to *Apophysomyces elegans*. Mayo Clin Proc. 2003;78:252–253.
29. Lewis RE, Albert ND, Kontoyiannis DP. Comparative pharmacodynamics of posaconazole in neutropenic murine models of invasive pulmonary aspergillosis and mucormycosis. Antimicrob Agents Chemother. 2014;58:6767–6772.
30. Ibrahim AS, Bowman JC, Avanessian V, et al. Caspofungin inhibits *Rhizopus oryzae* 1,3-beta-d-glucan synthase, lowers burden in brain measured by quantitative PCR, and improves survival at a low but not a high dose during murine disseminated zygomycosis. Antimicrob Agents Chemother. 2005;49:721–727.
31. Spellberg B, Fu Y, Edwards JE Jr, et al. Combination therapy with amphotericin B lipid complex and caspofungin acetate of disseminated zygomycosis in diabetic ketoacidotic mice. Antimicrob Agents Chemother. 2005;49:830–832.
32. Lewis RE, Leventakos K, Liao G, et al. Efficacy of caspofungin in neutropenic and corticosteroid-immunosuppressed murine models of invasive pulmonary mucormycosis. Antimicrob Agents Chemother. 2011;55:3584–3587.
33. Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what, and how? Clin Infect Dis. 2012;54 Suppl 1:S73–S78.
34. Ibrahim AS, Gebremariam T, Fu Y, et al. Combination echinocandin-polyene treatment of murine mucormycosis. Antimicrob Agents Chemother. 2008;52:1556–1558.
35. Gebremariam T, Alkhazraji S, Baldin C, et al. Prophylaxis with isavuconazole or posaconazole protect immunosuppressed mice from pulmonary mucormycosis. Antimicrob Agents Chemother. 2017;61:e02589-16.
36. Gebremariam T, Wiederhold NP, Alqarihi A, et al. Monotherapy or combination therapy of isavuconazole and micafungin for treating murine mucormycosis. J Antimicrob Chemother. 2017;72:462–466.
37. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood. 2011;118:1216–1224.
38. Ghadiali MT, Deckard NA, Farooq U, et al. Frozen-section biopsy analysis for acute invasive fungal rhinosinusitis. Otolaryngol Head Neck Surg. 2007;136:714–719.
39. Gleissner B, Schilling A, Anagnostopolous I, et al. Improved outcome of zygomycosis in patients with hematological diseases? Leuk Lymphoma. 2004;45:1351–1360.
40. Perfect JR. Treatment of non-*Aspergillus* moulds in immunocompromised patients, with amphotericin B lipid complex. Clin Infect Dis. 2005;40 Suppl 6:S401–S408.
41. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis. 1998;26:1383–1396.
42. Garbino J, Adam A. Use of high-dose liposomal amphotericin B: efficacy and tolerance. Acta Biomed. 2006;77 Suppl 4:19–22.
43. Revankar SG, Hasan MS, Smith JW. Cure of disseminated zygomycosis with cerebral involvement using high dose liposomal amphotericin B and surgery. Med Mycol. 2007;45:183–185.
44. Lewis RE, Albert ND, Liao G, et al. Comparative pharmacodynamics of amphotericin B lipid complex and liposomal amphotericin B in a murine model of pulmonary mucormycosis. Antimicrob Agents Chemother. 2010;54:1298–1304.
45. Stanzani M, Vianelli N, Cavo M, et al. Liposomal amphotericin B nephrotoxicity in patients with hematological malignancies: a retrospective cohort analysis. Antimicrob Agents Chemother. 2017;61:e02651-16.
46. Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. Br J Haematol. 1997.
47. Safdar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. Medicine (Baltimore). 2010;89:236–244.
48. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis. 2007;44:1289–1297.
49. Lanternier F, Poiree S, Elie C, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015;70:3116–3123.
50. Dekkers BGJ, Bakker M, van der Elst KCM, et al. Therapeutic drug monitoring of posaconazole: an update. Curr Fungal Infect Rep. 2016;10:51–61.
51. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother. 2006;50:126–133.
52. Raad II, Graybill JR, Bustamante AB, et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. Clin Infect Dis. 2006;42:1726–1734.
53. van Burik J-AH, Hare RS, Solomon HF, et al. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis. 2006;42:e61–e65.
54. Kraft WK, Chang PS, van Iersel MLPS, et al. Posaconazole tablet pharmacokinetics: lack of effect of concomitant medications altering gastric pH and gastric motility in healthy subjects. Antimicrob Agents Chemother. 2014;58:4020–4025.
55. Cornely OA, Haider S, Grigg A, et al Phase 3 Pharmacokinetic (PK) and Safety Study of Posaconazole (POS) IV in Patients (Pts) at Risk for Invasive Fungal Infection (IFI). 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2013. <https://www.aspergillus.org.uk/content/phase-3-pharmacokinetics-pk-and-safety-study-posaconazole-pos-iv-patients-pts-risk-invasive>.
56. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1–e60.
57. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis. 2007;44:2–12.
58. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16:828–837.
59. Spellberg B, Brass E. The VITAL study: case control studies are hypothesis-generating. Lancet Infect Dis. 2016;16:886.
60. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47:364–371.
61. Pagano L, Cornely OA, Busca A, et al. Combined antifungal approach for the treatment of invasive mucormycosis in patients with hematologic diseases: a report from the SEIFEM and FUNGISCOPE registries. Haematologica. 2013;98:e127–e130.
62. Kyvernitakis A, Torres HA, Jiang Y, et al. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. Clin Microbiol Infect. 2016;22:811.e811–811.e818.
63. Davoudi S, Anderlini P, Fuller GN, et al. A long-term survivor of disseminated *Aspergillus* and Mucorales infection: an instructive case. Mycopathologia. 2014.
64. Hamilton JF, Bartkowski HB, Rock JP. Management of CNS mucormycosis in the pediatric patient. Pediatr Neurosurg. 2003;38:212–215.
65. Raj P, Vella EJ, Bickerton RC. Successful treatment of rhinocerebral mucormycosis by a combination of aggressive surgical debridement and the use of systemic liposomal amphotericin B and local therapy with nebulized amphotericin–a case report. J Laryngol Otol. 1998;112:367–370.
66. Bitterman H. Hyperbaric oxygen for invasive fungal infections. Isr Med Assoc J. 2007;9:387–388.
67. Ferguson BJ, Mitchell TG, Moon R, et al. Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis. Rev Infect Dis. 1988;10:551–559.
68. John BV, Chamilos G, Kontoyiannis DP. Hyperbaric oxygen as an adjunctive treatment for zygomycosis. Clin Microbiol Infect. 2005;11:515–517.
69. Gil-Lamaignere C, Simitsopoulou M, Roilides E, et al. Interferon-gamma and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important Zygomycetes. J Infect Dis. 2005;191:1180–1187.
70. Barratt DM, Van Meter K, Asmar P, et al. Hyperbaric oxygen as an adjunct in zygomycosis: randomized controlled trial in a murine model. Antimicrob Agents Chemother. 2001;45:3601–3602.
71. Abzug MJ, Walsh TJ. Interferon-gamma and colony-stimulating factors as adjuvant therapy for refractory fungal infections in children. Pediatr Infect Dis J. 2004;23:769–773.
72. Hubel K, Dale DC, Liles WC. Therapeutic use of cytokines to modulate phagocyte function for the treatment of infectious diseases: current status of granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, and interferon-gamma. J Infect Dis. 2002;185:1490–1501.
73. Hubel K, Dale DC, Engert A, et al. Current status of granulocyte (neutrophil) transfusion therapy for infectious diseases. J Infect Dis. 2001;183:321–328.
74. Lewis RE, Georgiadou SP, Sampsonas F, et al. Risk factors for early mortality in haematological malignancy patients with pulmonary mucormycosis. Mycoses. 2014;57:49–55.
75. El-Shabrawi MH, Arnaout H, Madkour L, et al. Entomophthoromycosis: a challenging emerging disease. Mycoses. 2014;57 Suppl 3:132–137.
76. Gugnani HC. Entomophthoromycosis due to *Conidiobolus*. Eur J Epidemiol. 1992;8:391–396.
77. Gugnani HC. A review of zygomycosis due to *Basidiobolus ranarum*. Eur J Epidemiol. 1999;15:923–929.
78. Walker SD, Clark RV, King CT, et al. Fatal disseminated *Conidiobolus coronatus* infection in a renal transplant patient. Am J Clin Pathol. 1992;98:559–564.
79. Bigliazzi C, Poletti V, Dell'Amore D, et al. Disseminated basidiobolomycosis in an immunocompetent woman. J Clin Microbiol. 2004;42:1367–1369.
80. Mugerwa JW. Subcutaneous phycomycosis in Uganda. Br J Dermatol. 1976;94:539–544.
81. Martinson FD. Clinical, epidemiological and therapeutic aspects of entomophthoromycosis. Ann Soc Belg Med Trop. 1972;52:329–342.
82. Khan ZU, Khoursheed M, Makar R, et al. *Basidiobolus ranarum* as an etiologic agent of gastrointestinal zygomycosis. J Clin Microbiol. 2001;39:2360–2363.
83. El-Shabrawi MH, Kamal NM, Kaerger K, et al. Diagnosis of gastrointestinal basidiobolomycosis: a mini-review. Mycoses. 2014;57 Suppl 3:138–143.
84. Khan ZU, Prakash B, Kapoor MM, et al. Basidiobolomycosis of the rectum masquerading as Crohn's disease: case report and review. Clin Infect Dis. 1998;26:521–523.
85. Lyon GM, Smilack JD, Komatsu KK, et al. Gastrointestinal basidiobolomycosis in Arizona: clinical and epidemiological characteristics and review of the literature. Clin Infect Dis. 2001;32:1448–1455.
86. Yousef OM, Smilack JD, Kerr DM, et al. Gastrointestinal basidiobolomycosis. Morphologic findings in a cluster of six cases. Am J Clin Pathol. 1999;112:610–616.
87. Kimura M, Furuta T, Maekura S, et al. Eumycotic mycetoma of the lower leg. Rinsho Byori. 1997;45:801–804.
88. Guarro J, Aguilar C, Pujol I. In-vitro antifungal susceptibilities of *Basidiobolus* and *Conidiobolus* spp. strains. J Antimicrob Chemother. 1999;44:557–560.
89. Dworzack DL, Pollock AS, Hodges GR, et al. Zygomycosis of the maxillary sinus and palate caused by *Basidiobolus haptosporus*. Arch Intern Med. 1978;138:1274–1276.
90. Foss NT, Rocha MR, Lima VT, et al. Entomophthoramycosis: therapeutic success by using amphotericin B and terbinafine. Dermatology. 1996;193:258–260.
91. Gupta M, Narang T, Kaur RJ, et al. A prospective case series evaluating efficacy and safety of combination of itraconazole and potassium iodide in rhinofacial conidiobolomycosis. Int J Dermatol. 2016;55:208–214.
92. Kumaravel S, Bharath K, Rajesh NG, et al. Delay and misdiagnosis of basidiobolomycosis in tropical South India: case series and review of the literature. Paediatr Int Child Health. 2016;36:52–57.
93. Mandhan P, Hassan KO, Samaan SM, et al. Visceral basidiobolomycosis: an overlooked infection in immunocompetent children. Afr J Paediatr Surg. 2015;12:193–196.
94. Zabolinejad N, Naseri A, Davoudi Y, et al. Aelami MH. Colonic basidiobolomycosis in a child: report of a culture-proven case. Int J Infect Dis. 2014;22:41–43.
95. Rose SR, Lindsley MD, Hurst SF, et al. Gastrointestinal basidiobolomycosis treated with posaconazole. Med Mycol Case Rep. 2012;2:11–14.

**FIG. 258.1** **Mucormycosis agents.** Illustration of the major differentiating morphologic features of three of the most common agents of mucormycosis isolated from patients. Note the presence and location of the rhizoids and columella, as well as the shape of the sporangia. The infectious spores reside within the sporangia. *(Illustration by Lori Messenger.)*

**FIG. 258.2** **Mucormycosis incidence.** Incidence of mucormycosis over 6 decades by host population (A) and site of infection (B). *(Modified from Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases.* Clin Infect Dis*. 2005;41:634–653.)*

**FIG. 258.3** **Pathogenesis of invasive mucormycosis.**

**FIG. 258.4** **Sino-orbital involvement of mucormycosis.** (A) Orbital involvement in cancer patient. Note the periorbital ecchymosis and sanguineous discharge from the eye. (B) Rapid progression of orbital involvement with necrosis of nasal bridge in less than 24 hours. (C) Necrotic eschar on the hard palate of a cancer patient with rhinocerebral mucormycosis. *(Courtesy Drs. Gerald Bodey, George Viola, and Mona Shiekh Sroujieh, University of Texas, MD Anderson Cancer Center, Houston, TX.)*

**FIG. 258.5** **Radiographic findings in sinopulmonary mucormycosis.** (A) Left maxillary sinus air-fluid level is evident in this computed tomography (CT) scan that is indistinguishable from bacterial sinusitis. (B) Magnetic resonance image reveals T2 signal hyperintensity in the left pterygoid musculature *(arrow)* in conjunction with a left maxillary sinus air-fluid level. (C) Multiple heterogeneous nodular and consolidative lesions with a large pulmonary vessel infarct *(wedge)* and modest pleural effusions are shown in a cancer patient with pulmonary mucormycosis. (D) Contrast-enhanced CT scan demonstrates a cavity within a dense infiltrate in a patient with acute myelogenous leukemia and pulmonary mucormycosis. *(Courtesy Dr. Edith Marom, University of Texas, MD Anderson Cancer Center, Houston, TX.)*

**FIG. 258.6** **Cutaneous presentation of mucormycosis.** (A) Chronic, nonhealing ulcer with necrosis after traumatic inoculation. Cutaneous ecthyma gangrenosum lesions behind the ear (B) and face (C) of a neutropenic patient with disseminated mucormycosis. *(Courtesy Drs. Gerald Bodey and Saud Ahmed, University of Texas, MD Anderson Cancer Center, Houston, TX.)*

TABLE 258.1 Taxonomic Organization of the Most Common Agents of Mucormycosis and Entomophthoramycosis

|  |
| --- |
| **Mucormycosis** |
| *Rhizopus rhizopodoformis* *Rhizopus arrhizus (Rhizopus oryzae)* *Rhizopus microsporus* *Rhizomucor pusillus* *Rhizopus stolonifer* *Cunninghamella bertholletiae* *Apophysomyces elegans* *Saksenaea vasiformis* *Lichtheimia (Absidia) corymbifera* *Mucor circinelloides* *Mucor velutinosus* *Syncephalastrum racemosum* *Actinomucor elegans* *Cokeromyces recurvatus* *Mortierella wolfii* |
| **Entomophthoramycosis** |
| *Conidiobolus coronatus* *Conidiobolus incongruus* *Basidiobolus ranarum* |

TABLE 258.2 Patterns of Mucormycosis by Host Population

| **PREDISPOSING CONDITION** | **PREDOMINANT SITES OF INFECTION** |
| --- | --- |
| Diabetes mellitus | Rhinocerebral, sino-orbital, cutaneous |
| Malignancy (typically hematologic malignancy) | Pulmonary, sinus, cutaneous, sino-orbital, disseminated |
| Hematopoietic stem cell transplantation | Pulmonary, sinus, rhinocerebral, disseminated |
| Solid-organ transplantation | Sinus, cutaneous, pulmonary, rhinocerebral, disseminated |
| Intravenous drug use | Cerebral, endocarditis, cutaneous, disseminated |
| Malnutrition | Gastrointestinal, disseminated |
| Deferoxamine therapy | Disseminated, pulmonary, rhinocerebral, cerebral, cutaneous, gastrointestinal |
| Trauma | Cutaneous, ocular |

TABLE 258.3 Summary of in Vitro Antifungal Activity of Different Antifungal Drugs Against Mucorales (Data Are Adapted From Dannaoui)174

| **CLASS** | **MOLECULE** | **MIC50 (µg/mL)** | **INTERPRETATION** |
| --- | --- | --- | --- |
| Allylamines | Terbinafine | 0.06 to >16 | Variable activity, depending on species |
| Pyrimidine analogues | Flucytosine | >16 | Inactive |
| Polyenes | Amphotericin B | 0.03 to 2 | Active |
| Azole | Fluconazole Itraconazole Voriconazole Posaconazole Isavuconazole | >16 0.25 to 16 2 to >16 0.03 to 2 0.25 to 8 | Inactive Variable activity depending on species Not active Active, depending on species Active, depending on species |
| Echinocandins | Caspofungin Micafungin Anidulafungin | >8 >8 >8 | Inactive Inactive Inactive |