Mucormycosis and Entomophthoramycosis (Zygomycosis)

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Previously the term zygomycosis was used to refer to infections caused by fungi belonging to the phylum Zygomycota, class Zygomycetes, orders Mucorales and Entomophthorales. However, a more recent classification based on molecular phylogenetic studies of rRNA, tef1, and rpb1, has abolished the class Zygomycetes and instead distributes fungi previously in the phylum Zygomycota into the phylum Glomeromycota and four subphyla, including Mucoromycotina, Kickxellomycotina, Zoopagomycotina, and Entomophthoromycotina (Table 1) [1]. Therefore, the term zygomycosis, which has been used by clinicians and mycologists for decades, is no longer relevant to fungal taxonomy. Both terms, mucormycosis and zygomycosis, are used throughout this book, reflecting the recent changes in nomenclature and the slower evolution of clinical parlance.

Fungi of the subphylum Mucormycotina, order Mucorales, are distributed into six families, all of which can cause cutaneous and deep infections in immunocompromised patients (Fig. 1) [2]. In contrast, the subphylum Entomophthoromycotina, order Entomophthorales, contains two families of organisms that cause subcutaneous and mucocutaneous infections primarily in immunocompetent children (Fig. 1) [3]. Because infections caused by organisms of the order Mucorales differ both clinically and pathologically from infections caused by organisms of the order Entomophthorales, we use the term mucormycosis to refer to infections caused by organisms belonging to the order Mucorales and entomophthoramycosis for infections caused by organisms of the order Entomophthorales. This chapter will be devoted to the more common problem of mucormycosis, and a small section at the end of the chapter deals with entomophthoramycosis.

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Mycology

Fungi of the order Mucorales are classified into six different families based on morphologic analysis of the fungi, including the presence and location of rhizoids, the presence of apophyses, and the morphology of the columellae [3]. Other taxonomically relevant features include carbohydrate assimilation and the maximal growth temperature. Because the diseases caused by the different families of Mucorales are clinically indistinguishable from each other, laboratory confirmation of the identity of the causative agent is the only way to differentiate among these fungi. The identification of organisms isolated from patients with mucormycosis to the species level is necessary to clarify the epidemiology of this infection and may be helpful in predicting susceptibility to different antifungal drugs.

Fungi in the family Mucoraceae are isolated more frequently from patients with mucormycosis than any other family. *Rhizopus oryzae* (*Rhizopus arrhizus*) is the most common cause of infection, representing approximately 70% of all cases, followed by *Rhizopus microsporus* var. *rhizopodiformis* [2, 4]. Other, less frequently isolated species of the Mucoraceae family that cause a similar spectrum of infections include *Absidia corymbifera, Apophysomyces elegans, Mucor* species, and *Rhizomucor pusillus* [2, 5]. Other organisms, such as *Cunninghamella bertholletiae* in the Cunninghamellaceae family have been increasingly isolated from patients with pulmonary, disseminated, and cutaneous mucormycosis [6–9]. Additionally, *Saksenaea vasiformis* in the Saksenaceae family has been reported as a cause of cutaneous [10], subcutaneous [11, 12], rhinocerebral [13], and disseminated infections [14, 15]. Rare cases of mucormycosis

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Table 1 New taxonomy of fungi previously belonging to the phylum *Zygomycota* (Adapted from [1])

Rank	Taxon
Phylum	Glomeromycota
Subphylum	Mucoromycotina
Order	Mucorales, Endogonales, Mortierellales
Subphylum	Entomophthoromycotina
Order	Entomophthorales
Subphylum	Zoopagomycotina
Order	Zoopagales
Subphylum	Kickxellomycotina
Order	Kickxellales, Dimargaritales, Harpellales, Asellariales

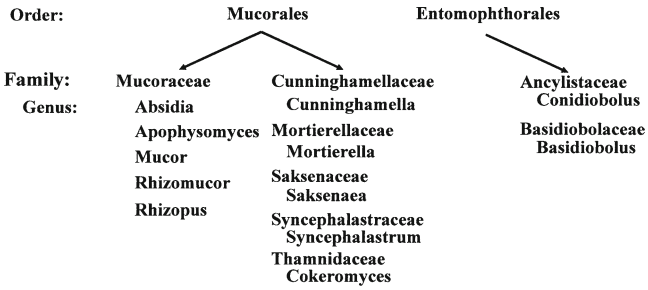

Fig. 1 Families of the order Mucorales (Adapted from [2])

have been reported due to *Cokeromyces recurvatus* in the Thamnidiaceae family [16], *Mortierella* species in the Mortierellaceae family [2] and *Syncephalastrum* species in the Syncephalastraceae family [17].

Epidemiology

Agents of mucormycosis are ubiquitous and thermotolerant organisms that usually grow in decaying matter, including bread, vegetables, fruits, and seeds. They can also be recovered from soil, compost piles, and animal excreta. Most of the Mucorales can grow and sporulate abundantly on any carbohydrate-containing source. Abundant growth with sporulation is usually seen in culture media within 2–5 days. The spores are easily airborne, and Mucorales are readily recovered as contaminants in laboratory cultures. Indeed, the ability of *R. microsporus* var. *rhizopodiformis* to grow on nonsterile wooden sticks used for culturing stool samples from immunocompromised patients has led to misdiagnosis of patients with gastrointestinal mucormycosis [18].

Members of the Mucorales cause both localized and disseminated infections in immunocompromised patients. Only rare case reports of invasive mucormycosis in apparently normal hosts have been described [19, 20], although local cutaneous infections may occur in patients who have had traumatic implantation of soil or plant material [21]. Allergic pulmonary disease does occur in immunocompetent hosts and reflects an acute hypersensitivity immune response illness rather than invasive disease [22, 23].

Mucormycosis is relatively uncommon in neutropenic patients compared to other fungal infections. However, there has been an alarming rise in the incidence of mucormycosis at major transplant centers. For example, at the Fred Hutchinson Cancer Research Center, Marr et al. described a greater than two-fold increase in the number of cases from 1985–1989 to 1995–1999 [24]. Kontoyiannis et al. described a similar increase in the incidence of mucormycosis at MD Anderson Cancer Center over a similar time span [25]. In fact, in high-risk patients the prevalence of mucormycosis has been described to be as high as 3% [26, 27], and up to 8% in autopsied patients with leukemia [28]. Because the number of iatrogenically immunocompromised patients continues to rise, it is likely that the incidence of mucormycosis will also increase [2, 4].

The major risk factors for mucormycosis include uncontrolled diabetes mellitus and other forms of metabolic acidosis, treatment with corticosteroids, especially in patients who have received an organ or bone marrow transplant, have experienced trauma or burns, have malignant hematologic disorders, or have received deferoxamine therapy to chelate iron in iron overload states. The underlying causes influence the clinical manifestations of the disease. For example, diabetics in ketoacidosis usually develop rhinocerebral mucormycosis, although other forms of the disease, such as pulmonary or disseminated infections may occur, whereas patients with malignant hematologic disease, lymphoma, or severe neutropenia usually develop pulmonary mucormycosis [4]. Both rhinocerebral and pulmonary mucormycosis are acquired through inhalation [2, 29]. Other routes of infection include direct implantation into skin, causing local cutaneous infection, and ingestion of contaminated food, which leads to gastrointestinal mucormycosis in highly immunocompromised patients and premature neonates.

Pathogenesis

Host Defenses

The pathogenesis of mucormycosis has been investigated in both in vitro and in animal models. Animal models have included mice or rabbits with mild diabetic ketoacidosis induced by streptozotocin or alloxan, cortisone-treated mice, neutropenic mice, and deferoxamine-treated animals. Inhalation of Mucorales spores by immunocompetent animals does not result in the development of mucormycosis [30]. In contrast, when the animals are immunosuppressed

by corticosteroids or by induction of diabetes, the animals die from progressive pulmonary and hematogenously disseminated infection [30, 31].

The ability of inhaled spores to germinate and form hyphae in the host is critical for establishing infection. Bronchoalveolar macrophages harvested from lungs of immunocompetent mice are able to ingest and inhibit germination of *R. oryzae* spores, preventing progression of the disease [30]. However, these bronchoalveolar macrophages have limited capacity to kill the organism; viable organisms can still be recovered from the phagolysosomes. In contrast, bronchoalveolar macrophages of immunosuppressed mice are unable to prevent germination of the spores in vitro or after intranasal infection [30].

Severely neutropenic patients are at increased risk for developing mucormycosis. In contrast, patients with the acquired immunodeficiency syndrome (AIDS) do not seem to be at increased risk for developing mucormycosis [3]. These findings suggest that neutrophils, but not necessarily T lymphocytes, are critical for inhibiting fungal spore proliferation. Recruitment of neutrophils to sites of infection occurs in response to fungal constituents and activation of the alternative complement pathway [32, 33]. Both mononuclear and polymorphonuclear phagocytes of normal hosts kill Mucorales by generating oxidative metabolites and the cationic peptides, defensins [30, 34, 35]. In the presence of hyperglycemia and low pH, as found in patients with diabetic ketoacidosis, phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and nonoxidative mechanisms [36]. The exact mechanisms by which ketoacidosis, diabetes, and corticosteroids impair the function of these phagocytes remain unknown. Furthermore, phagocyte dysfunction alone cannot explain the high incidence of mucormycosis in patients with diabetic ketoacidosis because the incidence of mucormycosis in these patients is increased much more than infections caused by other pathogens [3–5]. Therefore, Mucorales must possess unique virulence traits that enable the organism to survive in this subset of patients.

The Role of Iron in Pathogenesis

It has recently been discovered that a specific factor that uniquely predisposes patients in diabetic ketoacidosis to mucormycosis is the level of available unbound iron in serum [37, 38]. Iron is required by virtually all microbial pathogens for growth and virulence [39]. In mammalian hosts, very little serum iron is available to microorganisms because it is highly bound to host carrier proteins, such as transferrin [37]. Sequestration of serum iron is a major host defense mechanism against microbes in general and Mucorales in particular, because *Rhizopus* grows poorly in normal serum unless exogenous iron is added [37, 38]. Furthermore, the bacterial siderophore, deferoxamine, predisposes patients to *Rhizopus* infection by acting as a xenosiderophore, which supplies previously unavailable iron to the fungus [38]. The mechanism by which *Rhizopus* obtains iron from the iron-deferoxamine complex involves binding of this complex to the mold, followed by active reduction of the iron by the fungus, resulting in release of iron from deferoxamine and subsequent transport of the reduced iron intracellularly [40]. This transport is likely mediated by iron permeases. Administration of deferoxamine worsens survival of guinea pigs infected with *Rhizopus* but not *Candida albicans* [38, 40, 41]. Additionally, in vitro studies of radiolabeled iron uptake from deferoxamine in serum show that *Rhizopus* is able to incorporate eightfold and 40-fold more iron than is *Aspergillus fumigatus* and *C. albicans,* respectively [38].

As mentioned previously, patients with diabetic ketoacidosis are at high risk of developing rhinocerebral mucormycosis [3–5]. These patients have elevated levels of available iron in their serum, and such serum supports growth of *R. oryzae* at acidic pH (7.3–6.88) but not at alkaline pH (7.7–8.38) [37]. Sera that did not support *R. oryzae* growth at acidic pH had less available iron than sera that supported fungal growth. Furthermore, adding exogenous iron to sera allowed *R. oryzae* to grow profusely at acidic conditions but not at pH ≥ 7.4. Finally, simulated acidotic conditions decreased the iron-binding capacity of sera collected from normal volunteers, suggesting that acidosis temporarily disrupts the capacity of transferrin to bind iron, probably by proton-mediated displacement of ferric iron from transferrin [42].

Recent animal data showed that mice with diabetic ketoacidosis were protected from *Rhizopus* infection by administering iron chelators, such as deferiprone and deferasirox [43, 44], that are not utilized by *Mucorales* as xenosiderophores. These studies lend support to the hypothesis that increased susceptibility of patients with diabetic ketoacidosis to mucormycosis is likely due in part to an elevation in available serum iron.

Fungi can obtain iron from the host by using low-molecular-weight iron chelators (siderophores) or high-affinity iron permeases [39, 45]. Because the siderophores of *Rhizopus* species are very inefficient at obtaining iron from serum [38, 40], it is believed that these siderophores contribute very little to the ability of this organism to grow in patients who are receiving deferoxamine or who have diabetic ketoacidosis. The high-affinity iron permeases are able to transport serum iron intracellularly, and are therefore likely to be critical for the survival of the organism in susceptible hosts. Indeed recent data show that the high-affinity iron permease (*rFTR1*) is expressed by *R. oryzae* during murine infection. Inhibition of *rFTR1* gene expression by RNA-i or reduction of *rFTR1* copy number by gene disruption reduces the virulence of the fungus in animal models of mucormycosis [46].

A third mechanism by which fungi can obtain iron from the host is through utilization of hemin [47, 48]. The *Rhizopus* genome project revealed two homologues (RO3G_07326 and RO3G_13316) of the heme oxygenase (CaHMX1) [49]. These two *R. oryzae* homologues may enable *R. oryzae* to obtain iron from host hemoglobin, and might explain the angioinvasive nature of *R. oryzae*.

Mucorales–Endothelial Cell Interactions

A hallmark of mucormycosis is the virtually uniform presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis [4, 50]. This angioinvasion likely contributes to the capacity of the organism to hematogenously disseminate to other target organs. Therefore, damage of and penetration through endothelial cells or the extracellular matrix proteins lining blood vessels is likely a critical step in *R. oryzae*'s pathogenetic strategy. An earlier study showed that *R. oryzae* can adhere to the extracellular matrix laminin and type IV collagen [51]. More recently, it has been shown that *R. oryzae* spores and hyphae are able to damage human umbilical vein endothelial cells in vitro [52]. It has also been shown that injury requires adherence of the fungus to endothelial cells followed by invasion into the cells. Adherence to endothelial cells is believed to be mediated by a specific receptor since it was found to be saturable [52]. Glucose-regulated protein (GRP78) acts as a receptor which mediates penetration through and damage of endothelial cells by Mucorales. GRP78 (also known as BiP/HSPA5) is a member of the HSP70 protein family, and some of it is located on the cell surface [53]. It is a key regulator of the unfolded protein response (UPR) [54].

Interestingly, elevated concentrations of glucose and iron consistent with those noted during diabetic ketoacidosis enhanced surface GRP78 expression and resulting penetration through and damage of endothelial cells by Mucorales in a receptor-dependent manner. Mice with diabetic ketoacidosis have enhanced susceptibility to mucormycosis and have increased expression of GRP78 in the sinus, lungs, and brains when compared with normal mice. Anti-GRP78 immune serum protects mice in DKA from mucormycosis [55]. These observations provide novel insight into the etiology of the unique susceptibility of diabetic ketoacidosis patients to mucormycosis and could provide a foundation for novel therapeutic interventions.

Mycotoxins

Rhizopus species are also known for their ability to produce mycotoxins, such as the macrocyclic polyketide metabolite, rhizoxin, as well as the cyclic peptides, rhizonins A and B [56]. A recent study demonstrated that the mycotoxin rhizoxin is not biosynthesized by *Rhizopus* itself, but rather by an intracellular, symbiotic bacterium of the genus *Burkholderia* [57]. This bacterium is sensitive to antibiotics belonging to the fluoroquinolone family. For example, rhizoxin production is completely abrogated when *Rhizopus* is grown in media containing 40 μg/mL of ciprofloxacin [57]. Rhizoxin has long been known to be crucial to the plant pathogenic strategy of *Rhizopus,* but it does not appear to have a substantive role in causing mammalian disease. Organisms that have been rendered bacteria-free by ciprofloxacin treatment or those that cannot produce rhizoxin because of the absence of *Burkholderia* are still pathogenic in mouse and fruit fly models of infection [58].

Other putative virulence factors include the ability of *Rhizopus* to secrete lytic enzymes, including aspartic proteinases [59]. Additionally, *Rhizopus* species have an active ketone reductase system which may be an additional virulence factor that functions by enhancing growth in the acidic and glucose-rich environment seen in ketoacidotic states [60]. To date, none of these potential virulence factors have been definitively proven to be essential for the development of mucormycosis.

Clinical Manifestations

Based on clinical presentation and the involvement of a particular anatomic site, mucormycosis can be divided into at least five categories: (1) rhinocerebral, (2) pulmonary, (3) cutaneous, (4) gastrointestinal, and (5) disseminated.

Rhinocerebral

Rhinocerebral mucormycosis is the most common form of the disease, representing between one third to one half of all cases [61]. About 70% of cases of rhinocerebral (occasionally referred to as craniofacial) mucormycosis are found in diabetic patients with ketoacidosis [4, 62]. Rhinocerebral mucormycosis is increasingly being encountered in patients receiving high doses of corticosteroids, such as those with rheumatologic disorders, and those who have received an organ transplant [61, 63–65].

The initial presentation is often consistent with sinusitis, including facial pain, unilateral headache, proptosis, and soft tissue swelling. Fever is frequently, but not invariably, present. The infection may rapidly extend into the neighboring tissues. Infected tissues are initially erythematous, then violaceous, and ultimately black as tissue infarction develops (Fig. 2).

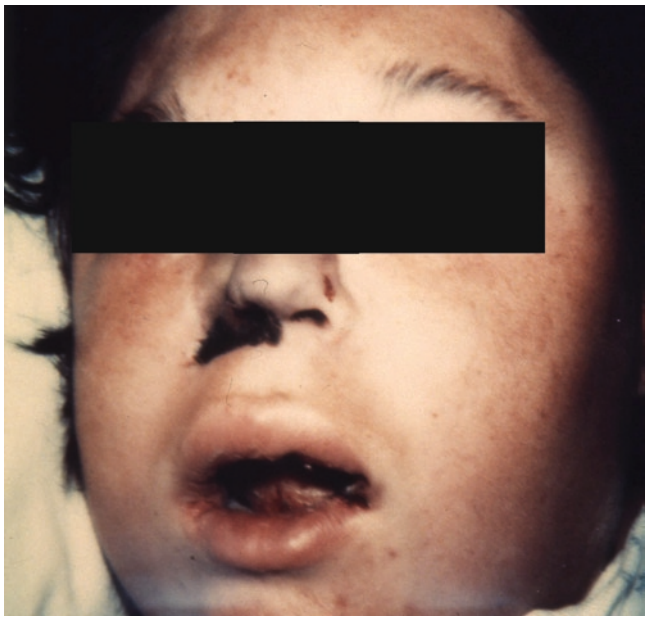

Fig. 2 Rhinocerebral mucormycosis in a pregnant woman who had diabetic ketoacidosis. Note bilateral swelling and infarction of skin of nose and infranasal tissue. There was also gangrenous ulceration of the palate

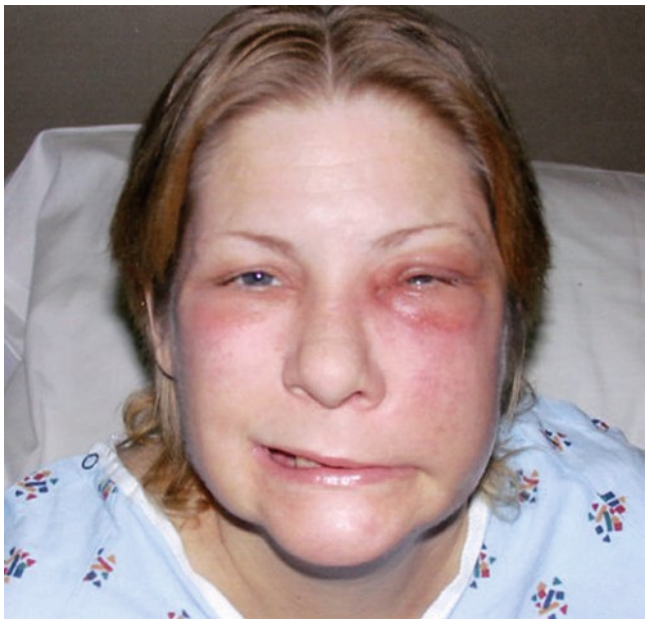

Fig. 3 Rhinocerebral mucormycosis in a patient who had diabetic ketoacidosis. Note swelling, erythema, proptosis, ptosis, and peripheral left facial nerve palsy

Infection can sometimes extend from the sinuses into the mouth and produce painful, necrotic ulcerations of the hard palate. If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in loss of extraocular muscle function, proptosis, and chemosis. Involvement of the optic nerve is manifested by blurred vision and eventually blindness. The trigeminal nerve may be affected, resulting in ptosis and pupillary dilation. Cranial nerve findings represent extensive infection and portend a grave prognosis (Fig. 3).

Infection can spread posteriorly from the orbit or sinuses to the central nervous system. Clinicians should consider the possibility of mucormycosis of the central nervous system in patients with diabetic ketoacidosis with mental status changes that persist after metabolic abnormalities have been corrected. The angioinvasive nature of the fungus may result in cavernous sinus and internal carotid artery thrombosis [66], and occasionally may lead to hematogenous dissemination of the infection [61, 67].

Prior to the availability of antifungal agents, rhinocerebral mucormycosis was almost universally fatal [67]. Although the mortality rate associated with rhinocerebral disease remains high, cure is likely when diagnosed early and treated aggressively with surgery and antifungal agents [68, 69]. Disease limited to the sinuses or orbit has a mortality rate of <40% with aggressive therapy, whereas disease extending into the central nervous system results in mortality rates >60%. The nature of the underlying disease and the reversibility of immune dysfunction are the most important determinants of survival. One study showed that among patients with rhinocerebral disease, survival was 75%, 60%, and 20% for patients with no underlying immunosuppression, diabetes, and immunosuppression, respectively [70].

Pulmonary

Pulmonary mucormycosis occurs most commonly in patients with profound and prolonged neutropenia, such as that noted in patients with leukemia or recipients of a hematopoietic stem cell transplant. Such patients have usually received broad-spectrum antibiotics for unremitting fever [24, 71]. Patients with diabetic ketoacidosis can also develop pulmonary mucormycosis, although infections in these patients may be less fulminant and follow a more subacute course than is typically seen in patients with neutropenia [72, 73]. Pulmonary mucormycosis may develop as a result of inhalation or by hematogenous or lymphatic spread. Symptoms include fever, dyspnea, and cough. Angioinvasion results in tissue necrosis associated with hemoptysis, which may be fatal if a large blood vessel is involved [74, 75]. If infection is not treated, hematogenous dissemination to the contralateral lung and other organs occurs frequently. Patients with untreated pulmonary mucormycosis usually succumb to complications of disseminated disease [73]. When it occurs in isolation, pulmonary mucormycosis associated mortality is approximately 50–70%; it is almost universally fatal if a manifestation of disseminated disease [73, 76].

Cutaneous

Cutaneous mucormycosis can occur following traumatic implantation of soil or plant material, such as occurs after motor vehicle accidents. In diabetic or immunocompromised patients, cutaneous lesions may arise at an insulin injection or catheter insertion site [77]. A large epidemic of cutaneous mucormycosis was reported in patients who had contaminated surgical dressings applied to their skin [78, 79]. Cutaneous mucormycosis may also occur in burn patients [80].

Although this form of disease usually arises from primary inoculation of the infection site, it sometimes is due to disseminated disease. These two routes of infection have distinct clinical presentations. Primary infection produces an acute inflammatory response with purulence, abscess formation, tissue swelling, and necrosis. The lesions may appear red and indurated, and often progress to black eschars. The necrotic tissue may slough and produce large ulcers. Primary cutaneous disease, which may be polymicrobial, is usually rapidly progressive even in the face of appropriate debridement and medical treatment. Occasionally, aerial mycelia may be visible on the surface of the cutaneous lesion. This form of cutaneous disease can be very invasive locally, and penetrate from the cutaneous and subcutaneous tissues into the adjacent fat, muscle, fascia, and bone. Cutaneous and subcutaneous disease may lead to necrotizing fasciitis, which has a mortality rate approaching 80% [81–83]. Secondary vascular invasion may also lead to hematogenously disseminated infection of the deep organs. When cutaneous mucormycosis results from hematogenously disseminated infection, the lesion typically begins as an erythematous, indurated, and painful cellulitis, progressing to an ulcerative lesion covered by a black eschar (Fig. 4).

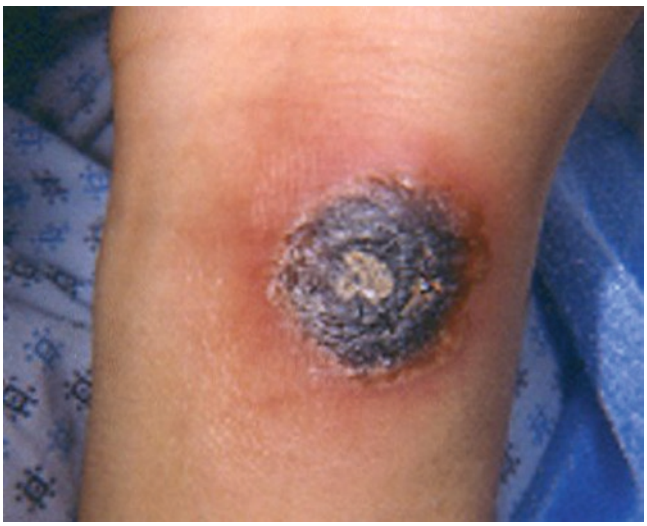

Fig. 4 Cutaneous mucormycosis in a patient who had acute leukemia. Note the black eschar with surrounding erythema. The lesion was quite painful (Courtesy of Dr. Dimitrios Kontoyiannis)

Gastrointestinal

Mucormycosis of the gastrointestinal tract is rare, but it is increasingly encountered in nosocomial settings. It is thought to arise from ingestion of the fungi. In the past, this was seen almost exclusively among patients who were extremely malnourished, especially infants and children [84, 85]. More recently, nosocomial infections have been described in neutropenic or other critically ill patients, sometimes resulting from primary contamination of a medication or from the contaminated wooden applicator sticks used to mix medication slurries. Symptoms of gastrointestinal mucormycosis are varied and depend on the affected site. Abdominal pain and symptoms of intestinal obstruction such as distention, nausea, and vomiting are the most common symptoms. Fever and hematochezia may also occur. The diagnosis is usually made by biopsy of the involved area during surgery or endoscopy.

Disseminated

Hematogenously disseminated mucormycosis may originate from any primary site of infection. Pulmonary mucormycosis in severely neutropenic patients has the highest incidence of dissemination. Less commonly, dissemination can arise from the gastrointestinal tract, the sinuses, or cutaneous lesions, particularly in burn patients. The most common site of dissemination is the brain, but metastatic lesions may be found in any organ, especially the spleen, heart, and skin. Cerebral infection following dissemination is distinct from rhinocerebral mucormycosis, and results in abscess formation and infarction. Patients may present with an insidious onset of neurologic symptoms, or with more sudden development of focal neurologic deficit, altered mental status, and coma. The mortality rate associated with dissemination to the brain approaches 100% [86]. With or without central nervous system involvement, disseminated mucormycosis has a mortality rate >90% [76]. Agents of Mucorales may cause infection in virtually any body site. Central nervous system involvement in the absence of sinus infection, endocarditis, and pyelonephritis occur occasionally, usually in the context of intravenous drug use [87–90]. Other reports have described mucormycosis in osteoarticular structures, mediastinum, trachea, superior vena cava, and as a cause of external otitis [91–97].

Diagnosis

A high index of suspicion is required to make the diagnosis of mucormycosis. Autopsy series demonstrate that up to half of cases are diagnosed postmortem [98, 99]. Because the

Mucorales are environmental isolates, establishing a definitive diagnosis requires a positive culture from a sterile site obtained by a needle aspirate or a tissue biopsy or histopathologic evidence of invasive disease [4]. A probable diagnosis of mucormycosis can be established by culture from a nonsterile site, such as sputum or bronchoalveolar lavage, in a patient with appropriate risk factors and clinical and radiographic evidence of disease.

Despite the fact that the Mucorales grow quite quickly on laboratory culture media, cultures may be negative in up to half of patients with mucormycosis. The primary reason for negative cultures from affected tissues is that the organism is killed during tissue grinding, which is routinely used to process tissue specimens for culture in clinical microbiology laboratories. When mucormycosis is a diagnostic consideration, the clinical microbiology laboratory should be notified so that tissue for culture may be placed in whole sections or cubes in the center of a culture plate, rather than subjected to routine homogenization prior to inoculation on artificial media.

There are no reliable serologic or skin tests for mucormycosis; the diagnosis is usually made by examination of biopsy or cytologic material. The characteristic histologic appearance is the presence of wide, ribbon-like, aseptate hyphae that branch at right angles (Fig. 5). The organisms are often surrounded by extensive necrotic debris. Other fungi including *Aspergillus, Fusarium, or Scedosporium* species may appear similar to Mucorales on biopsy, but these molds are usually thinner, septate, and branch at acute angles. The genus and species of the infecting organism are determined by morphologic identification and sporulation patterns of the fungi isolated in culture.

Routine imaging with CT may be an insensitive means of determining the extent of disease among patients with rhino-orbital-cerebral disease, sometimes demonstrating only sinus involvement [100]. MRI is more sensitive than CT scans for detecting orbital and CNS involvement [100]. Only rarely is a retro-orbital mass seen on CT scans among patients with orbital mucormycosis and proptosis.

CT scans are useful for early detection of pulmonary mucormycosis, particularly in patients with cancer. By logistic regression, pulmonary mucormycosis in patients with cancer could be distinguished from aspergillosis on the basis of the presence of sinusitis, multiple (≥10) nodules by CT scan, and pleural effusion [101]. Also, a recent retrospective study reported that seven of eight immunocompromised patients treated at a cancer center who had a "reverse halo" sign (focal area of ground-glass attenuation surrounded by a ring of consolidation) on chest CT scan had mucormycosis rather than infections with other molds [102]. The reverse halo sign was seen early in the disease course of these patients. Further refinement of radiographic techniques for distinguishing mucormycosis from other infectious and non-infectious diseases is an important area of future research.

The diagnosis of disseminated disease is made difficult because patients are usually ill with multiple comorbid conditions and virtually always have negative blood cultures. In the appropriate patient, evidence of infarction in multiple organs should suggest a diagnosis of mucormycosis. Other disseminated mycoses, especially aspergillosis, may present with an identical clinical picture. Patients with suspected disseminated mucormycosis should undergo a careful search for unexplained cutaneous lesions for biopsy.

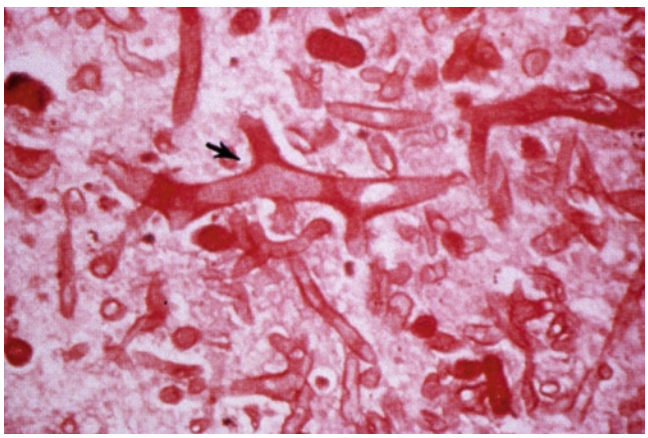

Fig. 5 Periodic acid–Schiff stain of excised tissue from the sinus of a patient with rhinocerebral mucormycosis. Note the wide, ribbon-like hyphae that branch at right angles and that do not show septae

Treatment

Four factors are critical for eradicating mucormycosis: rapidity of diagnosis; reversal of the underlying predisposing factors, if possible; appropriate surgical debridement of infected tissue; and appropriate antifungal therapy. Early diagnosis is important because small, focal lesions can often be surgically excised before they progress to involve critical structures or disseminate. Moreover, early initiation of polyene therapy within 5 days of diagnosis has been associated with improvement in survival [103]. Hence, establishing an early diagnosis of mucormycosis and early appropriate therapeutic intervention is critical to optimize long-term outcomes. Correcting or controlling predisposing problems is also essential for improving the treatment outcome. In diabetic ketoacidotic patients, hyperglycemia and acidemia should be corrected. Discontinuation of deferoxamine or immunosuppressive therapy, particularly corticosteroids, should be strongly considered when the diagnosis of mucormycosis is made.

Surgical debridement of the infected and necrotic tissue should be performed on an urgent basis. In rhinocerebral mucormycosis, early surgical excision of the infected sinuses

and appropriate debridement of the retro-orbital space can often prevent extension into the eye and obviate the need for enucleation. It is important to emphasize that during orbital surgery among patients with presumed mucormycosis, it is necessary to biopsy the extraocular muscles, since they may appear normal despite extensive fungal involvement. Repeated surgical exploration of the sinuses and orbit may be necessary to ensure that all necrotic tissue has been debrided and the infection has not progressed. Among patients with pulmonary mucormycosis, surgical treatment plus antifungal therapy greatly improves outcome compared to the use of antifungal therapy alone [73]. Moreover, surgery was found to be an independent variable predicting a favorable outcome in patients with mucormycosis [104].

Polyenes

Amphotericin B deoxycholate (AmB-d) is the only antifungal agent approved for the treatment of mucormycosis [3–5]. Because many Mucorales isolates are either relatively or highly resistant to AmB-d, high doses of this drug are required. AmB-d should be administered at 1.0–1.5 mg/kg/day initially. However, this dose is frequently associated with significant nephrotoxicity. Thus, lipid formulations of AmB have become preferred agents for this infection because they are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time when compared to AmB-d [100, 105]. Several recent studies demonstrate the efficacy of these agents. In one study, amphotericin B lipid complex (ABLC) resulted in a 71% success rate as salvage therapy for mucormycosis [106]. Primary treatment with liposomal amphotericin B (LAmB) was associated with a 67% (16/24) survival rate, compared to 39% (24/62) survival with AmB-d ($p=0.02$) in cancer patients with mucormycosis. [76] Additionally, animal studies have demonstrated that high-dose LAmB (15 mg/kg/day) is more efficacious than AmB (1 mg/kg/day) in treating diabetic ketoacidotic mice infected with *R. oryzae* [107].

Recent animal data suggest that LAmB may be preferred to ABLC for treating central nervous system mucormycosis. In a comparative pharmacokinetic study in rabbits, LAmB achieved brain tissue levels of >5-fold greater than ABLC [108]. While LAmB and ABLC are similarly effective in neutropenic mice, LAmB is superior to ABLC in mice with diabetic ketoacidosis, primarily due to superior clearance of the fungus from the brain [109]. A recent retrospective series in patients with rhino-orbital-cerebral mucormycosis receiving ABLC as primary therapy found that these patients had inferior outcomes when compared to patients receiving either AmB-d or LAmB, confirming these observations in animals [100].

Azoles

Itraconazole is the first marketed azole drug that showed promising in vitro activity against *Absidia,* but not against *Rhizopus* spp., the most common pathogens isolated from clinical cases [110]. Therefore, itraconazole plays almost no role in treating mucormycosis. Fluconazole and the second-generation broad-spectrum triazole, voriconazole, are not active against Mucorales in vitro [110]. Indeed the prophylactic and therapeutic use of voriconazole in transplant patients has been associated with breakthrough disseminated mucormycosis [27, 111–115]. In fact, a recent study demonstrated that in vitro pretreatment of *Mucorales* with voriconazole, increased the virulence of these organisms in murine and fly models of mucormycosis [31].

Posaconazole was approved recently by the Food and Drug Administration (FDA) for prophylaxis in patients with prolonged neutropenia and for stem cell transplant patients with severe GVHD and also for treatment of esophageal candidiasis. Posaconazole has enhanced in vitro activity against *Mucorales*, with reported MIC_{90} of 0.25–8 μg/mL, with *Rhizopus* spp. having the highest MIC (MIC_{90} 8 μg/mL) [110, 116–118]. In febrile neutropenic patients and in those with invasive fungal infections, oral posaconazole, 400 mg twice daily, results in serum levels consistently <1 μg/mL, with considerable patient-to-patient variability [119–122]. Therefore, pharmacokinetic/pharmacodynamic data raise concerns about the reliability of achieving adequate in vivo levels of oral posaconazole to treat mucormycosis, especially infection caused by *Rhizopus* species.

Animal data assessing the role of posaconazole in treating experimental mucormycosis raise concerns about the efficacy of this drug. For example, in neutropenic mice infected with *Mucor* species, posaconazole was significantly less effective than AmB-d [123]. Similarly, Dannaoui and colleagues [124] found that posaconazole was less effective than AmB-d in treating mice infected with *Rhizopus microsporus* or *Absidia,* and it had no activity in mice infected with *R. oryzae,* which causes >70% of clinical cases of mucormycosis [4, 100, 104]. In two more recent studies, posaconazole monotherapy was also no better than AmB-d placebo for treatment of *R. oryzae* infection in neutropenic or DKA mice [125, 126].

Based on the available animal data and the absence of clinical data, posaconazole monotherapy cannot currently be recommended as primary treatment of mucormycosis. In contrast, available clinical data from open-label salvage studies suggest that posaconazole is a reasonable option for patients with mucormycosis who are refractory to or intolerant of polyenes [127, 128]. It is also commonly used as "step-down" therapy for stable patients who have initially responded to a polyene, but there are no prospective studies exploring this approach to therapy.

Antifungal Combination Therapy

All approved echinocandins, including caspofungin, micafungin, and anidulafungin, have minimal activity against agents of mucormycosis when tested in vitro [129, 130]. However, it is known that *R. oryzae* has the 1,3 β-glucan synthase target enzyme for echinocandins [49], and this enzyme can be inhibited by these agents [131]. In the murine model of disseminated mucormycosis, caspofungin has limited activity against *R. oryzae* [131]. Furthermore, in diabetic ketoacidotic mice infected with *R. oryzae*, combination caspofungin plus ABLC therapy markedly improves survival rates compared to caspofungin alone or placebo [132]. Combination therapy with LAmB plus either micafungin or anidulafungin improves survival rates in neutropenic and diabetic ketoacidotic mice with disseminated mucormycosis [133]. The mechanism by which echinocandins improve the outcome of mucormycosis infection when combined with lipid formulations of AmB is unknown, but it could be related to the enhanced exposure of β glucan on the fungal surface, which in part results in enhanced immune stimulation [134, 136]. Alternatively, echinocandins might affect certain virulence factors of *Mucorales* that are as yet unidentified.

In a recent small retrospective study, combination therapy with lipid formulations of AmB plus caspofungin was associated with significantly improved outcomes for rhino-orbital-cerebral mucormycosis in diabetic patients compared to polyene monotherapy [100]. By multivariate analysis, only combination therapy was significantly associated with superior outcomes (OR = 10.9 for success vs. monotherapy, $p = 0.02$).

Because the data are very limited, further clinical studies are necessary to determine the usefulness of echinocandin combination therapy in patients with mucormycosis. If used in a combination regimen, dose escalation of echinocandins is not advisable due to possible paradoxical loss of efficacy, as has been noted in murine mucormycosis at doses ≥ 3 mg/kg/day [131, 133].

Iron Chelation Therapy

The iron chelators deferiprone and deferasirox have been shown to have activity in murine mucormycosis [43, 44]. Deferasirox, which is currently approved to treat iron overload in transfusion-dependent anemias [135], is fungicidal for clinical isolates of Mucorales in vitro, with an MIC_{90} of 6.25 μg/mL [136]. The drug exhibits time-dependent killing, with killing occurring at 12–24 h of drug exposure. Based on trough serum levels >15 μg/mL in patients treated with deferasirox at 20 mg/kg/day [137, 138], it should be feasible to maintain deferasirox serum levels in excess of the MICs of Mucorales. In diabetic ketoacidotic mice with disseminated mucormycosis, deferasirox is as effective as LAmB therapy, and combination deferasirox-LAmB therapy synergistically improves survival rates [136]. In particular, combination therapy results in a 100-fold decrease in brain fungal burden compared to monotherapy.

Based on these animal data, deferasirox was used successfully as salvage therapy in a patient with advanced rhinocerebral mucormycosis who had progressive brainstem disease despite LAmB therapy [139]. A study describing adjunctive therapy with deferasirox given to eight patients with mucormycosis suggested that the drug is safe and possibly efficacious, based on the observation that seven of eight patients survived the infection [140]. One study reported the failure of salvage deferasirox in a patient who had undergone partial colectomy to resect mucormycosis [141]. This failure might be attributed to the poor bioavailability of the oral iron chelator in the context of abdominal surgery.

Currently, a double-blind, randomized, placebo-controlled, phase II study of adjunctive deferasirox therapy (20 mg/kg/day for 14 days) with LAmB for mucormycosis is ongoing. Additional clinical data will be necessary to gain a more comprehensive safety and efficacy profile for this drug in combination with antifungals.

Posaconazole Combination Therapy

Two recent preclinical studies evaluated the efficacy of posaconazole combination therapy for murine mucormycosis. In the first study, Rodriguez et al. found that combining posaconazole with AmB-d enhanced the survival rate of neutropenic mice infected with *R. oryzae* only when compared to a subtherapeutic dose (0.3 mg/kg/day) of AmB-d monotherapy [126]. In contrast, combination therapy was not superior to a standard dose of AmB-d monotherapy (0.8 mg/kg/day). In the second study, combination posaconazole plus LAmB did not improve survival rates compared to LAmB monotherapy in either neutropenic or diabetic ketoacidotic mice with mucormycosis [125]. To date, no clinical studies have evaluated the combination of posaconazole and polyene for primary therapy for mucormycosis.

Hyperbaric Oxygen Treatment

Some case reports have suggested that hyperbaric oxygen may be a beneficial adjunct to the standard surgical and medical antifungal therapy of mucormycosis, particularly for

patients with rhinocerebral disease. In a small retrospective study of patients with rhinocerebral mucormycosis, two of six patients who received hyperbaric oxygen died, whereas four of seven patients who received only standard debridement and amphotericin B died. It is hypothesized that hyperbaric oxygen might be useful for treating mucormycosis in conjunction with standard therapy because higher oxygen pressure improves the ability of neutrophils to kill the organism [142]. Additionally, high oxygen pressure inhibits the germination of fungal spores and growth of mycelia in vitro [143].

Cytokine Treatment

Proinflammatory cytokines, such as interferon-gamma and granulocyte-monocyte colony-stimulating factor (GM-CSF), enhance the ability of granulocytes to damage the agents of mucormycosis [144]. Case reports have described survival of patients with mucormycosis treated with adjunctive recombinant G-CSF and GM-CSF or with recombinant interferon-gamma in conjunction with lipid formulations of AmB [145–149]. G-CSF-mobilized granulocyte transfusions have been increasingly used for refractory mycoses, including mucormycosis [150, 151]. The reported experience with granulocyte transfusions is limited to anecdotal reports, but such transfusions may be lifesaving in persistently neutropenic hosts with mucormycosis.

Entomophthoramycosis

Mycology

The order Entomophthorales includes two histopathologically similar, but clinically and mycologically distinct, genera: *Basidiobolus* and *Conidiobolus* [2, 3, 5]. Both basidiobolomycosis and conidiobolomycosis present mainly as subcutaneous infections in immunocompetent hosts. However, both of these infections occasionally disseminate in both immunocompetent and immuncompromised hosts [2]. Basidiobolomycosis is caused by *Basidiobolus ranarum.* Previous descriptions of this organism have used the synonyms *B. haptosporus, B. meristosporus,* or *B. heterosporus* [2]; however, *B. ranarum* is currently considered the preferred name. Infection with this organism tends to involve the trunk and limbs. In contrast, conidiobolomycosis (also known as rhinophycomycosis, rhinoentomophthoromycosis, or nasofacial zygomycosis) is caused by *Conidiobolus coronatus* or *Conidiobolus incongruous,* and primarily involves the nose and soft tissues of the face [152, 153].

Epidemiology

Basidiobolomycosis is predominantly a disease of childhood and adolescence and is only occasionally seen in adults [5]. In contrast, conidiobolomycosis almost always afflicts adults [154, 155]. Both diseases occur primarily in the tropical and subtropical regions of Africa and Southeast Asia [2]. Rare cases have been seen in other parts of the world. Although entomophthoramycosis occurs mainly in healthy individuals, some cases have occurred in immunocompromised hosts [156–158].

The agents of entomophthoramycosis are normally found in soil throughout the world. *Basidiobolus ranarum* is found in decaying vegetation, soil, and the gastrointestinal tracts of reptiles, fish, amphibians and bats [159]. Similarly, *C. coronatus* is found in soil, decaying vegetation, insects, and in the gastrointestinal contents of lizards and toads [2, 160, 161]. Although the agents of entomophthoramycosis are ubiquitous, clinically apparent infection is rare. Only 150 cases were estimated to occur worldwide in 1991 [162], raising the possibility that rather than a chance event, the individuals who develop this infection have a subtle defect in host immunity to this group of organisms.

The mode of transmission for *B. ranarum* is assumed to be through minor skin trauma and insect bites [163]. Fungal spores are found in bristles of mites and are probably carried by other insects. Infected insects are ingested by reptiles and amphibians, which subsequently pass the spores in their excreta [164]. *Basidiobolus ranarum* may be present on "toilet leaves" that are used for skin cleaning after a bowel movement. Thus, direct inoculation of the perineum may occur from these contaminated leaves. Consistent with this theory is the finding that the infection most commonly occurs in the buttocks, thigh, and perineum [163]. *Basidiobolus ranarum* occasionally causes rhinocerebral infections in hyperglycemic patients, suggesting that it may also be acquired by inhalation [156].

Conidiobolomycosis occurs eight times more frequently in males and is most common in individuals who work outdoors in the tropical and subtropical rain forests of Africa and Southeast Asia. The mode of transmission of conidiobolomycosis has not been clearly established. The predilection of the organism to infect the head and face suggests that the route of inoculation is via inhalation of spores or through minor trauma to the nose or face [154]. It is also possible that this infection is transmitted by insect bites [152].

Conidiobolomycosis is also a zoonotic infection, occurring in horses and mules [152].

Clinical Manifestations

Basidiobolomycosis typically presents as a chronic infection of the subcutaneous tissue of the arms, legs, trunk, or buttocks [165] and is characterized by the presence of firm painless nodular subcutaneous lesions that spread locally. The infection is slowly progressive if not treated, but may also heal spontaneously [166]. Although dissemination is uncommon [167], deeper invasion of the muscles beneath the subcutaneous infected areas [168] as well as widespread dissemination [169] have been reported. Rarely, *B. ranarum* infects the gastrointestinal tract, typically the stomach, duodenum, and colon [170–172]. Symptoms of gastrointestinal basidiobolomycosis include fever, abdominal pain, diarrhea, constipation, weight loss, and, less commonly, chills and rigors. Angioinvasive disease similar to that noted in mucormycosis has been described [169, 173] Polypoidal mass in the paranasal sinuses with extradural extension has been reported as a rare complication [174].

Infections with *Conidiobolus* present most commonly as chronic sinusitis. The infection initially manifests with swelling of the inferior nasal turbinates. Untreated, infection extends to the adjacent facial and subcutaneous tissues and the paranasal sinuses. Swelling of the nose, mouth, and perinasal tissue ensues, resulting in nasal congestion and drainage, sinus pain, and epistaxis [175]. Severe generalized facial swelling may develop [3]. The presence of subcutaneous nodules in the eyebrows, upper lip, and cheeks may be quite disfiguring, especially if there is regional lymph node involvement and subsequent lymphedema [176]. Rarely, infection can involve the pharynx and larynx, resulting in dysphagia and airway obstruction. Unlike mucormycosis, conidiobolomycosis usually does not spread to the central nervous system [167]. Disseminated infections are rare, but have been reported in both immunocompetent and immunocompromised patients [154].

Diagnosis

In endemic areas of entomophthoramycosis, basidiobolomycosis and conidiobolomycosis can most easily be distinguished from one another by the anatomic location of the infection and the age of the patient. The diagnosis is best made by biopsy of the infected subcutaneous or submucosal tissue. Both diseases have similar histopathology. The hyphae, which are broad, thin-walled, and occasionally septate, are best visualized with hematoxylin and eosin staining because of the presence of Splendore-Hoeppli eosinophilic material [167]. Other stains such as periodic acid–Schiff and Gomori methenamine silver are less effective in staining the Entomophthorales [3, 170]. Hyphae are surrounded by eosinophils, lymphocytes, and plasma cells. The presence of eosinophils is an important histopathologic finding for entomophthoramycosis. Angioinvasion with subsequent tissue necrosis and infarction are rarely seen [3]. The agents of entomophthoramycosis cannot be identified at the species level by histopathology; thus specimens must be cultured if species identification is to be performed.

Treatment

No single drug has been proven to be effective in treating all cases of entomophthoramycosis. Saturated solution of potassium iodide (SSKI), trimethoprim-sulfamethoxazole, AmB-d azoles, and a combination of these agents have been used with varying success. Because of the rarity of the infections, none of these treatment regimens have been directly compared. Furthermore, some cases of entomophthoramycosis may resolve without treatment. SSKI has traditionally been used in the treatment of entomophthoramycosis, with mixed clinical results [160, 177, 178] The mechanism of action of SSKI is not known. Therapy with SSKI should be administered for at least 3 months at 1.5–2.0 g daily. Trimethoprim-sulfamethoxazole has fewer side effects than SSKI; however, it must be administered at high doses for a longer period of time [179, 180]. Fluconazole [181] and itraconazole [182] have been used successfully to treat entomophthoramycosis, but there has been more experience with ketoconazole [152, 162, 179]. Anecdotally, months of continuous treatment with ketoconazole or multiple courses of shorter-course therapy are required for resolution of the infection [152, 179]. Amphotericin B is usually not the first choice of treatment, but is often used as salvage therapy. Some isolates of *B. ranarum* and *Conidiobolus* species are susceptible to AmB in vitro, while other isolates are resistant [183]. There are anecdotal reports of successful therapy with SSKI combined with trimethoprim-sulfamethoxazole [154], ketoconazole [152, 184], or fluconazole [152] in patients in whom single-drug therapy had failed. Terbinafine combined with either AmB-d or itraconazole has also been successful [185, 186] Experience with lipid formulations of AmB is limited.

In addition to antifungal therapy, surgical removal of accessible nodules and reconstruction of grossly deformed tissues should be performed when possible. Unfortunately, relapses of infection may occur following surgery [5].

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