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REVIEW

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Zygomycosis: the re-emerging fungal infection

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Abstract Invasive fungal infections are major medical complications in immunocompromised patients. The recent rise in the incidence of cancer and the increased use of newer medical treatment modalities, including organ transplantations, have resulted in growing numbers of highly immunosuppressed individuals. Although aspergillosis and candidiasis are among the most common invasive mycoses in such patients, there is evidence that the incidence of infectious diseases caused by Zygomycetes has risen significantly over the past decade. Patients with diabetes, malignancies, solid organ or bone marrow transplants, or iron overload and those receiving immunosuppressive agents, deferoxamine therapy, or broad-spectrum antimicrobial drugs are at highest risk for zygomycosis. This review details the emergence and importance of zygomycosis in current clinical practice and its manifestations and management. The etiologic species, pathogenesis and risk factors for zygomycosis are reviewed and updated. The clinical spectrum of zygomycosis is now broader, and it can be difficult to distinguish between mucormycosis and enthomophthoramycosis, both of which can manifest as disease ranging from a superficial infection to an angioinvasive infection with high mortality. Finally, the three-part treatment strategy (antifungal drugs, surgery, control of underlying diseases) is reviewed. Lipid formulations of amphotericin B are the antifungal agents of choice for treatment of zygomycosis. A novel antifungal triazole, posaconazole, has been developed and may become approved for treatment of zygomycosis. The clinical experience with adjunctive treatments like colony-stimulating factors, interferon-gamma, and hyperbaric oxygen therapy is still limited.

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Introduction

Zygomycosis is a term used to describe a group of fungal infections caused by pathogenic moulds belonging to the class Zygomycetes of the phylum Zygomycota [1]. The fungi in this class characteristically produce thick-walled resting spores called zygospores following gametangial fusion within a zygosporangium for their sexual reproduction [2]. Asexual reproduction of these fungi uses the nonmotile sporangiospores in the sporangia. The taxonomic classification of Zygomycetes and the terminology of diseases caused by this group of fungi have been confusing and are still in flux [3, 4]. The recent use of advanced molecular techniques has rearranged the classification of Zygomycetes. The term zygomycosis is currently used to broadly describe any diseases caused by the members of the class Zygomycetes. The moulds in this class comprise two fungal pathogenic groups of medical importance, the orders Mucorales and Entomophthorales. In fact, these two orders of fungi produce different clinical manifestations of human infections. Mucorales typically produce a group of acute-onset and relatively rapid, aggressive, fatal, angioinvasive diseases called mucormycoses, whereas Entomophthorales produce a group of diseases called entomophthoramycoses, which are more indolent and chronically progressive [5, 6]. In recent years,

however, it has been clearly shown that the geographic distribution and the invasiveness of the diseases caused by Entomophthorales, along with the range of infected hosts, have broadened. Entomophthorales can produce clinical syndromes indistinguishable from those caused by Mucorales, and it is impossible to differentiate these two orders of fungi based solely on histopathological examination or epidemiologic observations [7]. Zygomycosis is no longer an uncommon disease, due in part to the continued rise of diabetes and the increased use of immunosuppressive agents in the current era of advanced modern medicine.

Zygomycosis caused by Mucorales (mucormycosis)

Infection caused by fungal pathogens in the order Mucorales was formerly termed "phycomycosis", which is no longer used [1]. Although the majority of human cases of zygomycosis are caused by the Mucorales, the more recent term of zygomycosis is broader and more relevant when fungal cultures are not available or the fungal identification is not known, and thus the term zygomycosis is currently preferable to describe the angioinvasive diseases caused by this group of fungal pathogens.

Etiology of zygomycosis

The Mucorales, like other Zygomycetes, are mainly saprophytic, terrestrial, rapidly growing fungi. The Zygomycetes have the ability to assimilate carbohydrates and, importantly, are able to grow at temperatures greater than 37°C [7, 8]. Mucorales are true human opportunistic pathogens that have been classified into six families (Table 1). However, human pathogenicity of *Mortierella* spp. is no longer certain because the identification of *Mortierella* isolates in the two previous case reports of *Mortierella* infections was based solely on colony morphology and growth characteristics, and none of the isolates sporulated [9, 10].

The most common species causing angioinvasive zygomycosis is *Rhizopus arrhizus* (*Rhizopus oryzae*), followed by *Rhizopus microsporus* var. *rhizopodiformis* and *Rhizomucor pusillus* [6]. Approximately half of all zygomycosis cases are caused by *Rhizopus* spp. [11]. *R. arrhizus* is the most frequent cause of rhinocerebral forms of zygomycosis, whereas *R. microsporus* var. *rhizopodiformis* produces primarily cutaneous and gastrointestinal zygomycosis. *Absidia corymbifera* is the primary species isolated from the earliest case reports of zygomycosis and ranks as the second most common organism causing zygomycosis. *Mucor* spp. rank as the third most common etiology of this disease. *R. pusillus* is the only *Rhizomucor* species that causes diseases in humans and can be differentiated from other Mucorales by its unique thermophilic growth. The species *Cunninghamella bertholletiae* is the only member in its genus that has been proven to cause human disease, mainly pulmonary and disseminated zygomycosis, of which both forms are associated with a poor prognosis [12, 13].

In humans, most of the Mucorales are primarily opportunistic pathogens in immunosuppressed patients, but there have been some reports of zygomycosis in apparently healthy hosts caused by *C. bertholletiae* [14], *Saksenaea vasiformis* [15], and *Apophysomyces elegans* [16]. *Cokeromyces recurvatus* is an uncommon cause of localized human zygomycosis, and tissue invasion by this fungus has not yet been demonstrated. The only

Table 1 Etiologic agents of mucormycosis

Phylum Zygomycota
Class Zygomycetes
Order Mucorales
Family Mucoraceae/Absidiaceae
Genus *Absidia*
Species *Absidia corymbifera*
Genus *Apophysomyces*
Species *Apophysomyces elegans*
Genus *Mucor*
Species *Mucor circinelloides*
Mucor hiemalis
Mucor racemosus
Mucor indicus (*Mucor rouxianus*)
Mucor ramosissimus
Genus *Rhizomucor*
Species *Rhizomucor pusillus*
Genus *Rhizopus*
Species *Rhizopus arrhizus* (*Rhizopus oryzae*)
Rhizopus azygosporus
Rhizopus rhizopodiformis
Rhizopus stolonifer
Rhizopus schipperae
Rhizopus microsporus var. *microsporus*
Rhizopus microsporus var.*oligosporus*
Rhizopus microsporus var. *rhizopodiformis*
Family Cunninghamellaceae
Genus *Cunninghamella*
Species *Cunninghamella bertholletiae*
Family Mortierellaceae*
Genus *Mortierella*
Species *Mortierella wolfii*
Family Saksenaceae
Genus *Saksenaea*
Species *Saksenaea vasiformis*
Family Syncephalastraceae
Genus *Syncephalastrum*
Species *Syncephalastrum racemosum*
Family Thamnidaceae
Genus *Cokeromyces*
Species *Cokeromyces recurvatus*

*The fungi in this family are no longer counted as human pathogens
Adapted from Ribes et al. [2] and Prabhu and Patel [5]

confirmed case of zygomycosis caused by *Syncephalastrum* spp. was reported in a diabetic patient with a cutaneous infection [17].

Epidemiology of zygomycosis

The moulds of the class Zygomycetes are worldwide in distribution and can be found in soil and decaying organic matter [2]. In fact, wooden sticks used in the laboratory can harbor Zygomycetes and have been recognized as causes of pseudoepidemics of zygomycosis [18]. Major modes of transmission for development of human zygomycosis include inhalation, ingestion, and cutaneous exposure. Contamination of wounds, burns, and trauma sites with skin dehiscence is among the most important modes of transmission of zygomycosis in immunocompetent hosts. Ingestion of these fungi is usually the cause of gastrointestinal zygomycosis. The use of naturopathic medicine contaminated with *Mucor indicus* was linked to the development of hepatic zygomycosis following isolation and molecular genotyping of the causative strain [19]. Human-to-human transmission of zygomycosis has not yet been recognized.

Active population-based surveillance in San Francisco, USA, during 1992–1993 revealed that the incidence of zygomycosis was 1.7 cases per million persons per year [20]. A large series of 391 patients with hematologic malignancies and filamentous fungal infections reported by Pagano et al. [21] found that 45 (11.5%) patients were infected by Mucorales; moreover, these patients had a poorer prognosis than those with invasive aspergillosis. In one major cancer center, the incidence of zygomycosis steadily increased between 1985 and 1999 and paralleled the incidence of fusariosis. It was also found that zygomycosis tended to occur later after transplantation during graft-versus-host disease [22]. Furthermore, a recent study in organ transplant recipients showed that zygomycosis accounted for 5.7% of all opportunistic mould infections in these patients [23]. These reports show zygomycosis as an emerging non-*Aspergillus* mould infection of major importance.

Pathogenesis and risk factors

Host immunity in a healthy individual can prevent the germination of fungal spores after entering the host body unless the inoculum is too great, and therefore innate immunity prevents development of disease [24]. However, the macrophages in a diabetic or in a host with steroid-induced immunosuppression can lose their ability to inhibit spore germination and control disease progression. Underlying disease in the host is the most important risk factor for acquisition of zygomycosis. Table 2 lists the conditions and diseases that predispose patients to zygomycosis.

Table 2 Factors predisposing patients to zygomycosis

Diabetes mellitus
Diabetic ketoacidosis
Poorly controlled diabetes mellitus
Chronic metabolic acidosis
Renal failure
Chronic salicylate poisoning
Deferoxamine therapy
Iron overload
Immunosuppression
Neutropenia (due to malignancies or chemotherapy)
Corticosteroid therapy
Organ or hematopoietic cell transplantation
HIV infection
Skin or soft tissue breakdown
Burn
Trauma
Surgical wound
Miscellaneous
Intravenous illicit drug use
Neonatal prematurity
Malnourishment
Prolonged use of broad-spectrum antimocrobial agents

Adapted from Gonzalez et al. [7]

Diabetes mellitus and metabolic acidosis

Although zygomycosis can be observed in a metabolically controlled diabetic patient [25], diabetic patients with sustained hyperglycemia, particularly those with ketoacidosis, are more susceptible to zygomycosis [6, 7, 26]. In fact, diabetes mellitus as a predisposing factor has been reported in 36–88% of all zygomycosis cases [11, 27, 28]. Moreover, zygomycosis was found to be the first clinical manifestation of some patients who had undiagnosed diabetes mellitus [29]. Type 1, type 2, and secondary diabetes mellitus have all been reported as risk factors in patients with zygomycosis [29]. The most common clinical feature found in zygomycosis patients with diabetes mellitus is sinus disease (66%), followed by pulmonary zygomycosis (16%), whereas 19 and 60% of cancer patients had sinus disease and pulmonary disease, respectively [11]. The overall survival rate of diabetic patients with zygomycosis who undergo treatment is approximately 60%. The relatively easy management of acute complications of diabetes compared to the management of other immunocompromising conditions helps explain the lower mortality of zygomycosis associated with diabetes [11].

Serum from healthy individuals has the innate ability to inhibit growth of *Rhizopus* spp. [30]. On the other hand, investigators demonstrated that serum from diabetic ketoacidotic patients had the ability to stimulate fungal proliferation only while patients were acidotic. The simple addition of glucose, up to 1,000 mg/dl in nutrient broth, was not shown to stimulate growth of *R. oryzae* [30]. Thus, hyperglycemia per se did not seem to play a major role in

the pathogenesis of zygomycosis. On the other hand, acidosis has been shown to have an impact on the pathogenesis of zygomycosis. Artis et al. [30] demonstrated that acidosis disrupted the inhibitory activity of sera against fungal growth by interrupting the capacity of transferrin to bind iron from the fungal species, leading to a major defect in host defenses against Zygomycetes. Both decreased numbers of neutrophils and abnormal phagocytic cell function at the site of infection induced by diabetic ketoacidosis also likely play a role in the pathogenesis of zygomycosis during this condition [31]. Besides diabetic ketoacidosis, chronic metabolic acidosis due to other causes, such as chronic renal failure with uremia [32], chronic salicylate poisoning [33], and methylmalonicaciduria [34], has also been reported as a risk factor for zygomycosis.

Iron overload and deferoxamine therapy

Both iron overload, either transfusional or due to dyserythropoiesis, and deferoxamine therapy, used for the treatment of iron and/or aluminum overload in dialysis patients, were found to be risk factors for angioinvasive zygomycosis caused by Mucorales. A report of an international registry by Boelaert et al. [35] showed that 78% of dialysis patients with zygomycosis were being treated with deferoxamine, and the most common presentation of zygomycosis in patients receiving deferoxamine was the disseminated form (44%) followed by rhinocerebral disease (31%). Zygomycosis associated with deferoxamine therapy is highly fatal, with mortality reaching approximately 80% [1, 11, 35].

Besides the iron chelating agent, iron overload per se, with or without the concomitant use of deferoxamine, has also been recognized as a risk factor for zygomycosis [36–38]. It is likely that as underlying hematologic malignancies are controlled for longer periods of time with frequent transfusional support, there will be more high-risk patients with iron overload and thus a favorable clinical setting for zygomycosis. Maertens et al. [38] reviewed a series of five cases of invasive zygomycosis in 263 allogeneic bone marrow transplant recipients and demonstrated the association between severe iron overload and zygomycosis in these patients. The mean values of serum ferritin level, transferrin saturation, and number of transfused units of erythrocytes were 2,029 μg/l, 92%, and 52 units, respectively, and were significantly higher than those in the matched control group. Artis et al. [30] showed that sera from diabetic ketoacidotic patients with low plasma iron and high unbound iron-binding capacity of transferrin had the ability to inhibit the growth of *R. oryzae*. This study suggested that the capacity of transferrin to bind iron and therefore control iron availability might mediate the host innate defense by making the iron unavailable for the fungus to use as a growth factor. In vitro and in vivo studies have shown that iron and deferoxamine can enhance growth of Mucorales and improve the pathogenicity of *Rhizopus* spp. [39–41]. *Rhizopus* can synthesize and secrete a siderophore to bind iron and form a ferrirhizoferrin, which allows iron to be taken up by the fungus [39]. Moreover, deferoxamine itself can act as a siderophore to form the ferrioxamine complex, which will make iron available for use by *Rhizopus* [39–41]. There is also evidence that iron transfer has been observed between the ferrirhizoferrin and the apotransferrin, which then makes the iron unavailable to the fungus [39].

Immunosuppression

Zygomycosis in severely immunosuppressed patients is often fatal, with the mortality rate ranging from 68 to 100% [11, 42]. Prolonged neutropenia is one of the most important predisposing factors among this group of patients and is recorded in about 15% of zygomycosis cases. Pulmonary zygomycosis is the most common presentation in neutropenic patients, and disseminated zygomycosis is most often observed in the most profoundly immunosuppressed individuals [7, 31]. The incidence of zygomycosis in hematopoietic cell transplant recipients has been reported as 1–2% [38, 43, 44]. Morrison and McGlave [43] reported that 6 of 13 cases of zygomycosis in transplant recipients presented within 3 months of transplantation, but other reports revealed that the infection can occur within or after a year post transplantation [38, 45], especially during graft-versus-host disease [22]. Corticosteroid therapy is another primary risk factor that enhances a patient's susceptibility to zygomycosis by causing either defects in macrophages and neutrophils or steroid-induced diabetes [2]. Recently, human immunodeficiency virus (HIV) infection has also been recognized as a risk factor for zygomycosis, but most cases in HIV-infected patients are also associated with intravenous drug abuse [46–49].

Skin or soft tissue breakdown

Local trauma or burns resulting in breakdown of the skin integrity and/or subcutaneous tissue injuries with accidental inoculation of fungal spores to the injured sites can lead to cutaneous zygomycosis in both immunocompetent and immunocompromised hosts [50, 51]. The use of broad-spectrum antibiotics and/or topical antibacterial preparations in burn patients appears to increase the risk for cutaneous fungal infection, including zygomycosis [52]. Nosocomial cutaneous zygomycosis can also develop at surgical wound sites or at insertion sites of intravenous catheters.

Broad-spectrum azole use and other risk factors

Other important predisposing factors of zygomycosis include illicit intravenous drug use, neonatal prematurity, malnourishment, and prolonged use of broad-spectrum antimicrobial agents. Recently, there have been multiple

reports of a broad-spectrum antifungal agent, voriconazole, associated with development of zygomycosis in high-risk patients. In vitro studies showed that all Zygomycetes are resistant to voriconazole [53]. Since 2002, at least 23 cases of breakthrough zygomycosis associated with voriconazole use have been reported from many countries [54–61]. Of these 23 cases, 17 occurred in patients who underwent hematopoietic stem cell transplantation, 2 occurred in patients who had solid organ transplantation, and 4 occurred in patients with hematologic malignancies. Voriconazole was used for prophylaxis and treatment of invasive fungal infections in 14 and 9 patients, respectively. Duration of exposure to voriconazole ranged from 7 to 210 days, with one series reporting a median duration of exposure to voriconazole of 36 days [56]. The most common presentation was pulmonary zygomycosis in 13 patients, followed by disseminated zygomycosis in five patients, gastrointestinal zygomycosis in two patients, and rhinocerebral zygomycosis, trachea, and sinus infection in 1 patient each. The mortality rate of zygomycosis in this setting was approximately 83%.

Recently, Kontoyiannis et al. [62], in a case-controlled, prospective, surveillance study, compared 27 patients with zygomycosis with 54 patients with invasive aspergillosis and 54 high-risk patients without fungal infection. Of the 27 patients, only 15 received voriconazole; the remaining 12 received other antifungal agents preemptively or prophylactically, including caspofungin (six cases), amphotericin B (six cases), and itraconazole (one case). Breakthrough zygomycosis in the 12 patients who received other antifungal agents was clearly not related to voriconazole and may simply reflect the incidence of zygomycosis in this specific patient population relative to the degree of immunosuppression and other underlying risk factors.

Of the 27 cases of zygomycosis reported by Kontoyiannis et al. [62], 12 were documented on the basis of cultures alone and 6 by histopathological examination alone. Only 15 cases met the criteria for definite infection; the remaining cases were classified as probable zygomycosis. Arguably, a positive culture linked to positive histopathology is required for a definite diagnosis of zygomycosis; as discussed elsewhere in this review, a culture positive for Zygomycetes may not necessarily represent clinically significant disease, although this finding should be considered significant in a high-risk patient with predisposing factors for zygomycosis.

In the above study, voriconazole therapy was an independent risk factor for zygomycosis when zygomycosis patients were compared to patients with invasive aspergillosis, with the odds ratio (OR) being 20.3. When zygomycosis patients were compared with high-risk patients without fungal infection, voriconazole therapy was also found to be a risk factor for zygomycosis (OR=10.37) [62]. The authors concluded that, "It is tempting to speculate that the trends in the frequency of zygomycosis might reflect the increasing and prolonged use of oral voriconazole versus parenteral agents with activity against Zygomycetes, such as amphotericin B". However, it should be noted that the availability of voriconazole in oral and parenteral formulations permits the extended periods of antifungal prophylaxis/treatment that high-risk patients may require. In one recent report, voriconazole was administered prophylactically for 49–210 days before zygomycosis was diagnosed [58]; tolerability issues with agents such as amphotericin B generally mean that such prolonged courses of prophylaxis are not possible.

Another case-controlled study of 393 transplant recipients reporting to the Transplant Associated Infection Surveillance Network (TRANSNET) has shown that voriconazole is associated more frequently with breakthrough infections due to Zygomycetes and *Fusarium* spp. than with breakthrough infections due to *Aspergillus* spp. (OR=24.0) [63]. Finally, an echinocandin, caspofungin, is not particularly active against Zygomycetes and has been linked to a case of breakthrough pulmonary zygomycosis [64]. Interestingly, both Kontoyiannis et al. [62] and the TRANSNET data showed that the increase in the incidence of zygomycosis in the population studied was accompanied by a significant decrease in the incidence of aspergillosis [63].

Establishing a direct link between voriconazole use and an increase in the incidence of zygomycosis is quite complex. The vast majority of patients reported to have zygomycosis while using voriconazole were hematopoietic stem cell transplantation patients who were treated aggressively for graft-versus-host disease and received high doses of steroids, which is a known predisposing factor for zygomycosis. Additionally, the increase in the incidence of zygomycosis was initially observed prior to the introduction of voriconazole. Thus, a study of 5,589 patients who underwent hematopoietic stem cell transplantation in a cancer research center during 1985–1999 showed that zygomycosis occurred in 29 patients and was the second most common type of non-*Aspergillus* mould infection and followed fusariosis in numbers of cases. In an earlier study, Kontoyiannis et al. [65] compared the incidence of zygomycosis at MD Anderson Cancer Center between the periods 1989–1993 and 1994–1996 prior to the introduction of voriconazole and showed that the incidence of this disease was on the rise (approximately 2.5-fold increase between the two periods).

Furthermore, the incidence of zygomycosis definitely increased during the late 1990s in another study [22]. Kauffman [66] discussed possible reasons for the increase in the incidence of zygomycosis, including environmental factors, changes in transplantation procedures and other immunosuppression practices, and voriconazole use. Although environmental factors were dismissed as unlikely, it was suggested that transplantation and immunosuppression practices have evolved over the last decade, as graft-versus-host disease has become an increasingly severe problem for patients after transplantation. Moreover, infections are occurring later after transplantation. The apparent association of voriconazole use and zygomycosis is likely because voriconazole has broad-spectrum antifungal activity for severely immunosuppressed patients,

but it has no activity against the Zygomycetes. Moreover, the patients described by Siwek et al. [59] (and one patient described by Marty et al. [56]) had commenced therapy with this antifungal agent, and several patients were treated with high dosages, which likely exerted selective pressure for growth of resistant organisms. The mechanism linking voriconazole use and the increase in zygomycosis is unknown. The simplest explanation is that voriconazole prevents or treats *Aspergillus* infections, and the persistently immunosuppressed patient lives longer to eventually become colonized and then infected with a Zygomycete.

Despite uncertainty about the mechanism of this risk, from a clinical standpoint clinicians must be aware that high-risk patients on voriconazole can develop zygomycosis.

Clinical manifestations of zycomycosis

Rhinocerebral zygomycosis

Rhinocerebral zygomycosis describes an infection that originates in the paranasal sinuses and extends to the brain. The most common Mucorales species for this form of zygomycosis is *R. arrhizus*. Rhinocerebral zygomycosis is the most common manifestation of zygomycosis and occurs in nearly half of all zygomycosis cases reported in the literature [67, 68]. Rhinocerebral zygomycosis is most commonly associated with diabetes, although immunocompromised patients with other conditions can be at risk for this form of zygomycosis. There have also been reports of rhinocerebral zygomycosis in immunocompetent individuals, with *A. elegans* being the most common causative organism in this setting [69–72]. Overall mortality is around 62% in rhinocerebral zygomycosis and 16% in sinus infections without cerebral involvement [11].

Rhinocerebral zygomycosis generally manifests with sequential involvement of nose, sinuses, eyes, and brain. Early signs and symptoms may include fever, malaise, nasal congestion or pain, nasal serosanguinous discharge, occasional dark blood-tinged rhinorrhea or epistaxis, unilateral facial pain or swelling, and headache [73, 74]. Nasal ulcerations can occur, the frequency of which ranges from 38 to 74% [29, 67]. A painful black necrotic eschar on the palate or nasal mucosa is a classical diagnostic sign. However, the absence of this finding should not exclude the possibility of zygomycosis. In fact, clinicians must realize that, for a better prognosis, the diagnosis should be made as soon as possible and before this characteristic sign presents. When disease progresses, symptoms and signs can include periorbital swelling, orbital cellulitis, blurred vision or visual loss, external ophthalmoplegia, diplopia, ptosis, proptosis, chemosis, eyelid gangrene, retinal detachment, and endophthalmitis [29, 75, 76]. In cases of severe disease, patients may have cranial neuropathies and/or altered consciousness, bone destruction, retinal artery thrombosis, cavernous sinus thrombophlebitis, frontal lobe necrosis, cerebral abscess, basilar artery aneurysm, and internal carotid artery thrombosis [77–79].

Sinus roentgenograms and cerebrospinal fluid (CSF) findings are nonspecific and seldom helpful. Computed tomography (CT) and magnetic resonance imaging (MRI) are more useful for revealing abnormal soft tissue, involvement around the nerve sheaths, and bone destruction as well as for identifying the entire extent of disease [80, 81].

Pulmonary zygomycosis

Pulmonary zygomycosis is most often seen in patients with hematologic malignancies and severe neutropenia. In a review of pulmonary zygomycosis, 37% of patients had leukemia or lymphoma, whereas 32% had diabetes mellitus [82]. On the other hand, among zygomycosis patients with malignancies, 60% had pulmonary zygomycosis [11]. The overall mortality rate in patients with pulmonary zygomycosis is 76%, but it is higher in severely immunosuppressed patients [11].

Clinical manifestations of pulmonary zygomycosis cannot be easily distinguished from those of pulmonary aspergillosis. Patients may present with fever and cough. Hemoptysis, pleuritic chest pain, and pleural effusion can present as well but are less common. However, massive and potentially fatal hemoptysis can occur if the major pulmonary blood vessels are invaded [83–85]. Pulmonary zygomycosis may progress to invade the adjacent organs of the chest wall, such as the mediastinum and pericardium [86, 87]. Chest radiographs of patients with pulmonary zygomycosis are nonspecific and are also indistinguishable from those of patients with pulmonary aspergillosis. Radiologic findings include infiltration, consolidation, nodules, cavitation, atelectasis, effusion, thickening of the posterior tracheal band, hilar or mediastinal lymphadenopathy, and normal findings [87–89]. The air crescent sign can be observed and is similar to that seen in pulmonary aspergillosis [90, 91]. A recent study of CT scan features in 45 patients with hematologic malignancies who had pulmonary zygomycosis or invasive pulmonary aspergillosis found that the presence of multiple (≥10) nodules and pleural effusion at the initial CT scan were independent predictors of pulmonary zygomycosis. The differences in the frequency of masses, cavities, halo sign, and air crescent sign are insignificant between pulmonary zygomycosis and invasive pulmonary aspergillosis [92]. In rare circumstances, zygomycosis can present as an endobronchial or tracheal lesion, especially in diabetics. Endobronchial zygomycosis can cause airway obstruction, resulting in lung collapse, and can also lead to invasion of hilar blood vessels with subsequent massive hemoptysis.

Cutaneous zygomycosis

The major mode of acquiring cutaneous zygomycosis is inoculation of traumatic skin wounds or burns [50, 51, 93]. The most common Zygomycetes involved in cutaneous zygomycosis include *R. oryzae* and *R. rhizopodiformis*.

Although cutaneous zygomycosis affects patients with diabetes, leukemia, and organ transplantation, it is also the most common form observed in normal hosts and is associated with the lowest mortality rate of 10% [11]. Clinical features of cutaneous zygomycosis range from superficial skin structure involvement such as plaques, skin swelling, pustules, cellulitis, blisters, nodules, ulcerations, and echthyma gangrenosum-like lesions to deeper infections such as necrotizing fasciitis, osteomyelitis, and disseminated infection [5–7, 94]. Following the onset of cutaneous zygomycosis, the disease can progress slowly or rapidly. Cutaneous zygomycosis that develops after hematogenous dissemination usually results in erythematous and painful cellulitis with central necrosis and eschar [42].

Gastrointestinal zygomycosis

This form of zygomycosis, while rare, is usually fatal, with mortality being about 85% [11]. Disease can be acquired by ingestion of the pathogens in contaminated foods such as fermented milk or bread products. Hosts susceptible to gastrointestinal zygomycosis include malnourished children and individuals with hematologic malignancies, diabetes mellitus, or a history of corticosteroid use.

Gastrointestinal zygomycosis can occur in any part of the alimentary system, but the stomach is most commonly affected, followed by the colon and the ileum [95–97]. Gastrointestinal zygomycosis can also involve the liver, the spleen, and the pancreas. The fungi can invade through the bowel wall and blood vessels, resulting in bowel perforation, peritonitis, or massive gastrointestinal hemorrhage, which is the major cause of death [98, 99]. Symptoms and signs of gastrointestinal zygomycosis include fever, abdominal pain, abdominal distension, nausea, vomiting, diarrhea, hematemesis, melena, and hematochezia.

Disseminated zygomycosis

Zygomycosis of one organ can spread hematogenously to other noncontiguous organs and thus contribute to the disseminated form of zygomycosis. Severely immunosuppressed patients and patients receiving deferoxamine therapy are among those at greatest risk [5, 7, 35, 100]. Without appropriate treatment, all patients with disseminated zygomycosis die [100]. A fatal case of fulminant myocarditis has been recently reported as a serious complication of disseminated zygomycosis [101]. The most common organ associated with dissemination is the lung, and the most common site of spread is the brain [42]. The pathology in this setting usually produces neurological manifestations distinct from those of rhinocerebral zygomycosis. A metastatic skin lesion is an important hallmark to allow early diagnosis.

Other clinical manifestations of zygomycosis

Isolated cases of cerebral zygomycosis have been typically observed in patients who used intravenous drugs, which led to hematogenous dissemination. Isolated abscesses or infections of the kidney, mastoid, oral mucosa, bone, bladder, and ear caused by Mucorales have also been reported rarely. Furthermore, endocarditis occurring principally on and around prosthetic valves and peritonitis in patients receiving peritoneal dialysis have also been reported.

Diagnosis of zycomycosis

Histopathology

A definitive diagnosis of zygomycosis caused by Mucorales can be made by histopathological examination with or without isolation of the fungus from the same site. Histopathological examination of the tissues affected by Mucorales typically shows characteristic broad, hyaline, ribbon-like, wide-angled branching, pauciseptate irregular fungal hyphae accompanying tissue necrosis and angioinvasion of the fungi (Fig. 1) [102]. Tissue invasion by the fungal hyphae as seen by microscopy is essential to establish the diagnosis [103]. Tissue histopathology can be evaluated by a routine hematoxylin and eosin stain, but fungal elements can be better seen by staining them with Gomori methenamine-silver (GMS), periodic acid-Schiff (PAS), or Calcoflour White stain [2, 6]. Perineural invasion is found in 90% of tissues that contain nerves. The inflammatory responses can be neutrophilic, granulomatous, pyogranulomatous, or absent [102]. Fungal hyphae can also be examined directly using a potassium hydroxide preparation of tissue specimen or bronchoalveolar lavage fluid. Discovery of fungal elements in this specimen from an immunocompromised host is considered significant [104]. A fluorescent staining procedure using an optical brightener to directly stain specimens has been developed. This technique can be performed by preparing the clinical specimens with potassium hydroxide for maceration of the specimens and then staining with Calcofluor White, Blankofluor, or Uvitex and finally examining the fungi by fluorescent microscope. This procedure can be used with a fresh specimen or can be applied to Gram-stained microscopic mount. Zygomycetes are easily identified by this simple procedure, and this improved staining procedure would be suitable for use in the diagnosis of zygomycosis when there is a small number of organisms or a limited amount of tissue [105].

Culture

Blood cultures in all forms of zygomycosis are usually negative. Furthermore, even when fungal hyphae are seen in tissue specimens, fungal cultures may not be positive. However, it is important that clinicians attempt to collect

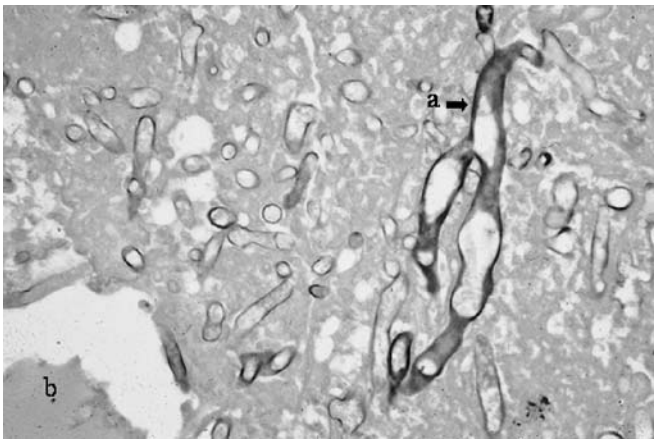

Fig. 1 Histopathological evidence of invasive zygomycosis: presence of tissue necrosis and angioinvasion invasion by pauciseptate, broad, irregular, hyaline fungal hyphae. **a**, fungal hyphae; **b**, necrotic tissue

many proper clinical specimens for fungal cultures to get a high-yield result because Mucorales are sometimes difficult to distinguish from other filamentous fungi in histopathological examination. Specimens should be collected from sterile sites, if possible, with a strictly aseptic technique. A large amount of tissue from an infarcted area is preferable to send for culture, and tissue should not be ground up or extensively minced since it may reduce the likelihood of recovering a viable fungus in culture [26]. Given the rarity of fungal septum, Mucorales are considered relatively vulnerable clinical specimens. Therefore, the specimens sent for culture should be plated as fast as possible. Refrigeration of the specimens is not recommended because it may decrease the yield of positive cultures. All Mucorales grow rapidly on most fungal media such as Sabouraud dextrose agar incubated at 25–30°C. These fungi are sensitive to the protein inhibitor, cycloheximide, and therefore this antimicrobial agent should not be added to the fungal media for recovery of Zygomycetes [1, 106]. Contamination of clinical specimens by these fungi is not uncommon because the small size of sporangiospores (approximately 6.6 μm) allows easy dissemination by the airborne route. Particles of this size may remain airborne even with very slight movements in air; consequently, these spores may contaminate clinical samples. Therefore, growth of Zygomycetes in culture may not represent clinically significant invasive disease. However, isolation of Mucorales from a sterile site or repeated positive cultures of the fungi from a nonsterile site is considered significant in a high-risk patient with predisposing factors for acquisition of zygomycosis. Positive cultures from nonsterile specimens should be interpreted with caution and will require correlation between the finding and the clinical situation.

Antifungal susceptibility testing

The standard antifungal susceptibility testing for Zygomycetes, specifically *R. arrhizus*, is the broth microdilution assay proposed by the Clinical and Laboratory Standards Institute (CLSI) [107]. However, with these fungi it is often difficult to get accurate and consistent endpoints. Limited data showed good agreement between the E test and the broth microdilution test in certain circumstances [108]. Since the interpretive MIC breakpoints have not yet been defined for Zygomycetes and the correlation between clinical response and MIC values for a given strain are uncertain [109], the use of antifungal susceptibility testing in zygomycosis for routine clinical decisions is not recommended at this time.

Zygomycetes are resistant to many antifungal drugs used to treat systemic mycoses, including flucytosine (5-FC), ketoconazole, fluconazole, voriconazole, and the echinocandins. However, Zygomycetes have variable susceptibility to itraconazole and terbinafine [53, 110–112]. Amphotericin B is effective against most pathogenic Zygomycetes and the MIC50 and MIC90 of the isolates are 0.25 and 0.5 μg/ml, respectively [53]. Posaconazole, a new investigational triazole, has been shown to possess direct antifungal activity against Zygomycetes. The reported MIC90 of posaconazole in a study of 36 Zygomycetes isolates was 1 μg/ml [112]. *Rhizopus* spp. are significantly less susceptible to itraconazole, posaconazole, terbinafine and amphotericin B than *Absidia* spp., and are also less susceptible than *Mucor* spp. to amphotericin B. Terbinafine appears to be more active against *R. microsporus* than against *R. oryzae* [112]. The MIC90 of posaconazole was highest for *Rhizopus* spp., at 8 μg/ml, whereas it was lowest for *S. vasiformis*, at 0.125 μg/ml [53].

Combinations of antifungal agents against Zygomycetes have been tested in vitro for 35 isolates of Zygomycetes, including *Rhizopus* spp. and *Absidia* spp. Synergism was seen for amphotericin B plus rifampin, amphotericin B plus terbinafine, and terbinafine plus voriconazole, whereas the amphotericin B plus 5-FC combination was not synergistic [110]. No antagonism was seen in any of the combinations studied. The potential role of combination therapy with caspofungin has been raised in a report that showed caspofungin to exhibit inhibitory activity against the *R. oryzae* 1,3-beta-D-glucan synthase [113]. However, reports of the efficacy of combination treatment of caspofungin with other antifungal agents have not yet been validated and cannot be recommended at present [114–116].

Molecular diagnosis

Molecular techniques for detection of Zygomycetes by polymerase chain reaction or other methods are not widely available and are reserved primarily for research purposes [117]. In fact, a recent molecular technique that used the MicroSeq D2 large-subunit ribosomal DNA sequencing kit to detect filamentous fungi had a high misidentification rate

among the Mucorales [118]. However, another panfungal polymerase chain reaction method that employed serial serum samples was used for the diagnosis of pulmonary mucormycosis caused by *C. bertholletiae* [119]. New techniques in the molecular identification of Zygomycetes need to be further developed and validated before they are used in clinical practice.

Serological tests

Development of serological tests for diagnosis of zygomycosis by means of antigen and/or antibody detection has been attempted. Antibodies to Zygomycetes can be detected by enzyme-linked immunosorbent assays (ELISAs) and double diffusion [2]. Immunoblot analyses have also been used to detect *R. arrhizus* antigens [120]. However, these serological tests for zygomycosis cannot be recommended without further clinical evaluation and are not available for routine use at this time.

Treatment

The prognosis of patients with zygomycosis due to Mucorales can be poor. Therefore, attempts to make an early diagnosis in a high-risk patient are encouraged, and treatment should be initiated quickly. Treatment of zygomycosis is through a multi-modality approach with an equally important three-point strategy that includes (a) antifungal therapy, (b) surgery, and (c) management of comorbid factors and adjunctive treatments for improving host response.

Antifungal therapy

Studies in non-neutropenic mice showed that itraconazole was inactive against *R. microsporus* but it significantly reduced mortality in mice infected with *A. corymbifera* or *A. elegans*. Terbinafine was also ineffective against *R. microsporus* and *A. corymbifera* in a study of non-neutropenic mice [121]. The survival rate of mice treated with amphotericin B following infection with *R. microsporus*, *A. corymbifera*, or *A. elegans* was between 90 and 100% [121]. A recent study found that survival of mice with diabetic ketoacidosis and *R. oryzae* infection was prolonged with low-dose but not high-dose caspofungin [113]. In a study of nonimmunocompromised mice with experimental disseminated zygomycosis treated with posaconazole, Dannaoui et al. [122] reported that posaconazole had no effect against *R. oryzae* but showed partial efficacy against *A. corymbifera* and a clear dose-response effect against *R. microsporus*. A study in neutropenic mice by Sun et al. [123] also revealed that posaconazole prolonged the survival and reduced the tissue burden of mice infected with *Mucor* spp.

The mortality of zygomycosis has been reduced since amphotericin B became clinically available. Most of the clinical experience in the treatment of zygomycosis has been with amphotericin B. In the past, amphotericin B deoxycholate was usually given at high daily doses. However, renal toxicity was a major side effect of this conventional drug. Lipid preparations of amphotericin B are safer than amphotericin B deoxycholate for long-term administration of amphotericin B and, in our opinion, represent first-line therapy. Three lipid formulations of amphotericin B are clinically available: liposomal amphotericin B, amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD). Lipid formulations of amphotericin B seem to be at least as active as amphotericin B deoxycholate, but they cause less nephrotoxicity. This advantage allows the antifungal therapy to be administered at higher dosages. These lipid formulations of amphotericin B have been used in the treatment of zygomycosis with consistently successful outcomes [124–127] and therefore are considered as drugs of choice for this disease [128]. ABLC has been reported to be an effective antifungal treatment in many invasive and refractory non-*Aspergillus* mould infections such as zygomycosis [129]. Furthermore, there have been reports of successful medical treatment with ABLC without surgical therapy in patients with rhinocerebral zygomycosis [130], isolated renal zygomycosis [131], and isolated cerebral zygomycosis [132]. In a study of 64 patients with zygomycosis treated with ABLC, Larkin and Montero [133] reported an overall success rate of 72%, with a 64% success rate in patients with disseminated disease. Amphotericin B lipid formulations should be used in a dose starting at 5 mg/kg/d, although higher doses will be needed occasionally. The duration of antifungal treatment should be determined on an individual basis, but therapy usually continues for at least 6–8 weeks. To clarify the optimal duration of amphotericin B treatment for zygomycosis, a retrospective review of zygomycosis cases treated with amphotericin B is recommended. The duration of the lipid amphotericin B therapy remains an evolving issue that will be further impacted when the possibility of sequential therapy with posaconazole becomes a reality.

The first human case of zygomycosis due to *Rhizopus* spp. successfully treated with posaconazole was reported in a diabetic patient with a dual heart/kidney transplantation [134]. Furthermore, a study of posaconazole efficacy in 23 patients with hematologic malignancies or hematologic stem cell transplantation and refractory zygomycosis revealed an overall successful response of approximately 70% [135]. Posaconazole has only been studied as an oral suspension and is not yet approved by the U.S. Food and Drug Administration (FDA) for general clinical use [136, 137]. It is clear that posaconazole may have a useful role in the management of zygomycosis, but whether it will be used as primary therapy, in cases refractory to treatment with lipid formulations of amphotericin B, or in sequential treatment with lipid formulations of amphotericin B awaits more clinical experience. However, it is likely that this agent will be useful in the management of zygomycosis.

Surgery

Because of the aggressive nature of the disease when vascular invasion and infarction of tissue are present and the difficulty in eradicating these fungi with medical treatment only, surgical debridement is crucial and highly recommended and must be done without delay. Repeated removal of necrotic tissue or aggressive surgical measures such as enucleation or exenteration of the eye resulting in organ disfiguration may be required for life-saving control of the infection. Surgical decisions regarding the extent of surgical debridement will need to be a "bedside" decision, but debridement should be aggressive. A CT or MRI scan prior to surgery is helpful for evaluating the need for surgical margins as well as for post-surgical evaluation. Intraoperative frozen sections also help determine the extent of involved tissues and tissue margins. Conditions such as low platelet counts or other bleeding problems must be corrected with sufficient transfusions of platelets or other blood components before the patient promptly undergoes surgical intervention. Unfortunately, bleeding problems can limit the surgical option in some cases. The higher survival rate of patients with zygomycosis who undergo combination medical and surgical treatment is well documented [82, 138].

Management of comorbidity and adjunctive treatments

Correction of metabolic disturbances and reversal of immunosuppression is as essential as the other therapeutic measures discussed above for successful management. In diabetic ketoacidotic patients, hyperglycemia and acidosis must be corrected to the normal condition as soon as possible. Immunosuppressive drugs and corticosteroids should be discontinued, if possible, or at least drug dosages should be decreased. Since many previous reports have shown an association between the predisposing conditions and a high mortality, the ability to correct these comorbid factors will predict a patient's prognosis.

Many adjunctive measures have been proposed for improving immunity and include the use of granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor, leukocyte transfusions, use of interferon-gamma, and hyperbaric oxygen treatment. Gil-Lamaignere et al. [139] reported that incubation of polymorphonuclear leukocytes with interferon-gamma and granulocyte-macrophage colony-stimulating factor alone or in combination for 22 h increased the polymorphonuclear leukocytes-induced hyphal damage of *R. oryzae*, *R. microsporus*, and *A. corymbifera*. Granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor have been used as an adjunctive treatment in some cases of zygomycosis with favorable outcomes [140, 141]. However, considering the small number of cases of zygomycosis that are reported to have successful treatment with these cytokines and the low likelihood of a randomized control trial of this disease being conducted, colony-stimulating factors and interferon-gamma are not recommended for routine use, but consideration of their use will need to be a bedside decision in case of a patient failing treatment with conventional therapy or one at very high risk for failure. The usefulness of leukocyte transfusions for treatment of zygomycosis remains uncertain, and such treatment might be harmful [142]. Adjunctive hyperbaric oxygen therapy, which can directly impact the growth of Zygomycetes, has been used successfully for adjunctive treatment of zygomycosis in a small number of patients without randomization to a control group [143]. This treatment has not been studied vigorously for efficacy and cannot be routinely recommended at this time.

Zygomycosis caused by Entomophthorales (entomophthoramycosis)

Agents of the Entomophthorales comprise two pathogenic genera, *Conidiobolus* and *Basidiobolus* (Table 3), that produce diseases called conidiobolomycosis and basidiobolomycosis, respectively. These pathogens typically cause chronic nonangioinvasive subcutaneous infections in immunocompetent individuals. However, emergence of outbreaks of invasive disease with these pathogens, including disseminated disease, has been noted [144, 145].

Cases of conidiobolomycosis have been reported from tropical Africa, South America, Central America, and Asia [5, 8, 146]. Reports of basidiobolomycosis are mainly from the tropical areas of Africa and Southeast Asia and from the tropical and subtropical regions of Asia, Australia, and South America [5, 8, 147]. Conidiobolomycosis is uncommon in children, whereas 88% of basidiobolomycosis cases were reported in patients under 20 years of age [148].

Conidiobolomycosis

Rhinofacial conidiobolomycosis is the most common type of infection caused by *Conidiobolus coronatus*. Symptoms and signs may begin with unilateral nasal obstruction, nasal

Table 3 Etiologic agents of entomophthoramycosis

Phylum Zygomycota
Class Zygomycetes
Order Entomophthorales
Family Ancylistaceae
Genus *Conidiobolus*
Species *Conidiobolus coronatus*
Conidiobolus incongruus
Conidiobolus spp.
Family Basidiobolaceae
Genus *Basidiobolus*
Species *Basidiobolus ranarum*
(*Basidiobolus haptosporus*)

Adapted from Ribes et al. [2] and Prabhu and Patel [5]

discharge, epistaxis, sinus tenderness, and swelling of the nose, upper lip, and face. As disease progresses, face disfiguration resulting from swelling can occur. The disease usually involves subcutaneous tissue as a granulomatous infection without bone destruction or skin ulceration, and the clinical course is slowly progressive [6, 149]. Systemic symptoms are usually absent, but disseminated conidiobolomycosis has been reported [145]. Diseases caused by *Conidiobolus incongruus* are extremely rare but are very aggressive.

Basidiobolomycosis

Infections caused by *Basidiobolus ranarum* involve primarily subcutaneous tissue. Basidiobolomycosis usually has a chronic progressive clinical course. Clinical features include a painless well-circumscribed subcutaneous nodule with firm consistency. Edema can occur at the involved sites. Skin lesions can be painful with disease progression. No bone involvement has been noted, and the skin that covers the nodule is usually normal. These granulomatous lesions are usually confined to subcutaneous tissue without adjacent organ involvement, although lymph node enlargement or muscle involvement has rarely been described [2, 147]. Commonly affected body parts are buttock, thigh, trunk, and, rarely, other parts of the body [147]. Clinical features of gastrointestinal basidiobolomycosis are usually nonspecific and indistinguishable from other chronic abdominal diseases. Patients may present with abdominal pain, nausea, vomiting, diarrhea, or abdominal mass. Besides subcutaneous and gastrointestinal infection, disseminated basidiobolomycosis in an immunocompetent host has also been reported [144].

Diagnosis

Characteristic histopathological findings of entomophthoramycosis usually comprise broad fungal hyphae with sparsely found septum surrounded by eosinophilic granular material (Splendore–Hoeppli phenomenon) that is not usually observed in diseases caused by Mucorales [147, 150, 151]. Peripheral eosinophilia may be present, and fungal culture may be negative.

Treatment

No standard treatment regimen is available for entomophthoramycosis. *Conidiobolus* spp. were more resistant than *Basidiobolus* spp. to all antifungal agents tested [152]. Antifungal agents used to treat entomophthoramycosis include potassium iodide, miconazole, ketoconazole, itraconazole, fluconazole, terbinafine, and amphotericin B, with varying success in clinical outcomes [147, 153–157]. No clinical data for newer triazoles such as voriconazole, posaconazole, or caspofungin are available.

Surgical treatment, in combination with medical therapy, for removal of the nodules and reconstructive surgery is also useful. Despite the lack of standard treatment, however, patients with an invasive manifestation of zygomycosis caused by Entomophthorales, such as disseminated or invasive disease, should be treated as aggressively as those with invasive infection caused by Mucorales [153].

Conclusion

Zygomycosis is no longer an uncommon fungal infection, since its incidence, especially in immunosuppressed and diabetic individuals, has increased during the past decade. The emergence of zygomycosis as a more common infection has not been clearly understood, although it has been linked to many factors such as the increased use of immunosuppressive drugs, novel cancer treatment interventions, environmental factors, and the use of broad-spectrum antimicrobial agents. The two formerly distinct diseases caused by Zygomycetes, mucormycosis and entomophthoramycosis, are now indistinguishable on the basis of their clinical manifestations and epidemiology because the clinical spectrum of zygomycosis has been broadened. Both Mucorales and Entomophthorales can cause an infectious disease with clinical presentations that range from a superficial infection to a lethal angioinvasive disease. A three-point strategy in the treatment of zygomycosis is essential and includes surgery, antifungal therapy, and management of comorbid factors and adjunctive treatments. Lipid formulations of amphotericin B are preferable for treatment of zygomycosis, and there has been more clinical experience with ABLC. A novel investigational triazole, posaconazole, has been recently introduced as a potentially effective antifungal treatment for zygomycosis, and it is likely to continue to receive acceptance for use in the management of zygomycosis. Entomophthoramycosis is a rare infection distributed in certain areas of tropical and subtropical regions. No standard treatment of entomophthoramycosis is currently available. Investigation of antifungal activity against Entomophthorales with newer or developing antifungal agents is needed for successful management of entomophthoramycosis.

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