REVIEW

Mucormycosis: an emerging disease?

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ABSTRACT

Mucormycosis is the third invasive mycosis in order of importance after candidiasis and aspergillosis and is caused by fungi of the class Zygomycetes. The most important species in order of frequency is *Rhizopus arrhizus* (*oryzae*). Identification of the agents responsible for mucormycosis is based on macroscopic and microscopic morphological criteria, carbohydrate assimilation and the maximum temperature compatible with its growth. The incidence of mucormycosis is approximately 1.7 cases per 1000 000 inhabitants per year, and the main risk-factors for the development of mucormycosis are ketoacidosis (diabetic or other), iatrogenic immunosuppression, use of corticosteroids or deferoxamine, disruption of mucocutaneous barriers by catheters and other devices, and exposure to bandages contaminated by these fungi. Mucorales invade deep tissues via inhalation of airborne spores, percutaneous inoculation or ingestion. They colonise a high number of patients but do not cause invasion. Mucormycosis most commonly manifests in the sinuses (39%), lungs (24%), skin (19%), brain (9%), and gastrointestinal tract (7%), in the form of disseminated disease (6%), and in other sites (6%). Clinical diagnosis of mucormycosis is difficult, and is often made at a late stage of the disease or post-mortem. Confirmation of the clinical form requires the combination of symptoms compatible with histological invasion of tissues. The probable diagnosis of mucormycosis requires the combination of various clinical data and the isolation in culture of the fungus from clinical samples. Treatment of mucormycosis requires a rapid diagnosis, correction of predisposing factors, surgical resection, debridement and appropriate antifungal therapy. Liposomal amphotericin B is the therapy of choice for this condition. Itraconazole is considered to be inappropriate and there is evidence of its failure in patients suffering from mucormycosis. Voriconazole is not active *in vitro* against Mucorales, and failed when used *in vivo*. Posaconazole and ravuconazole have good activity *in vitro*. The overall rate of mortality of mucormycosis is approximately 40%.

Keywords Amphotericin B, emerging, Mucorales, mucormycosis, zygomycetes

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INTRODUCTION

Mucormycosis, the third invasive mycosis in order of importance after candidiasis and aspergillosis, is a disease that may be caused by several species of different genera (Table 1). The term 'mucormycosis' is used throughout this review of infections caused by Mucorales.

The class Zygomycetes is divided into two orders, Mucorales and Entomophthorales. Members of the order Mucorales are the aetiological agents of the disease traditionally known as 'mucormycosis', a fulminant disease with high rates of morbidity and mortality that mainly affects immunocompromised patients. However, species of the order Entomophthorales are responsible for the chronic subcutaneous disease observed in immunocompetent patients in tropical and sub-tropical regions [1].

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MICROBIOLOGY

Fungi belonging to the order Mucorales fall into six families (i.e., Mucoraceae, Cunninghamellaceae, Mortierellaceae, Saksenaceae, Syncephalastraceae and Thamnidaceae), with Mucoraceae

Table 1. Classification of the aetiological agents responsible for mucormycosis

Family	Genus	Species
Mucoraceae	*Absidia*	*A. corymbifera*
	Apophysomyces	*A. elegans*
	Mucor	*M. circinelloides*
		M. hiemalis
		M. racemosus
		M. ramosissimus
		M. rouxianus
	Rhizopus	*R. pusillus*
		R. arrhizus
		R. azygosporus
Cunninghamellaceae	*Cunninghamella*	*C. bertholletiae*
Mortierellaceae	*Mortierella*	
Saksenaceae	*Saksenaea*	*S. vasiformis*
Syncephalastraceae	*Syncephalastrum*	*S. racemosum*
Thamnidaceae	*Cokeromyces*	*C. recurvatus*

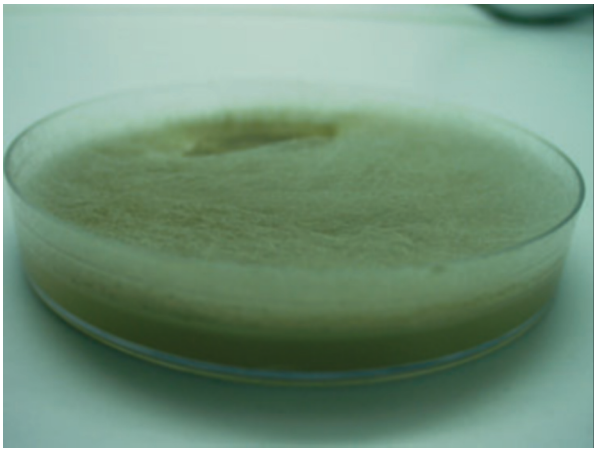

Fig. 1. Macroscopic appearance of a positive culture for Mucorales.

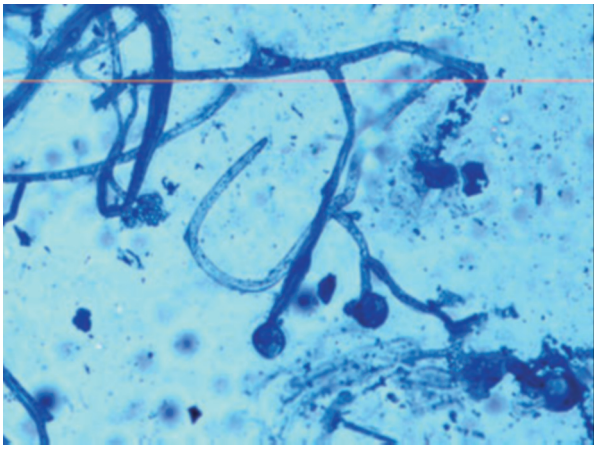

Fig. 2. Microscopic details of Mucorales.

being the most frequent cause of mucormycosis. The most important species in order of frequency are: *Rhizopus arrhizus* (*oryzae*), *Rhizopus microsporus* var. *Rhizopodiformis*, *Rhizomucor pusillus*, *Cunninghmaella bertholletiae*, *Apophysomyces elegans*, and *Saksenaea vasiformis* [2–6].

Mucorales grow well on both non-selective and selective media. Growth is rapid, with mycelial elements expanding to cover the entire plate in only a few days. The mycelium is described as fibrous or 'cotton candy-like' and its growth is so vigorous that the group has come to be known as 'lid lifters'.

Identification of the agents responsible for mucormycosis is based on macroscopic and microscopic morphological criteria, carbohydrate assimilation and the maximum temperature compatible with its growth. Macroscopic criteria are helpful in establishing a presumptive identification, which should be confirmed by microscopic analysis after staining. Important macroscopic features are a hyaline appearance, vigorous growth, light colouration on the reverse side of the plate (tan to yellow for most species) and variable degrees of colouration on the sporulating surface of the colonies (from pure white to tan, brown, grey or even black). Morphological speciation is microscopic and is based on the demonstration of important fungal elements. The family Mucoraceae may be divided on the basis of the morphology of the predominant asexual spore-producing structures (sporangium producers, sporangiola producers and merosporangium producers). Species can be differentiated by elements such as rhizoids, stolons and columella, which are usually visualised in the microbiology laboratory on lactophenol cotton blue-stained slides. Hyphae are wide, non-septate and measure 10–20 μm in diameter, with branches which separate from the main body at almost 90° angles (Figs 1 and 2).

EPIDEMIOLOGY

The incidence of mucormycosis is approximately 1.7 cases per 1000 000 inhabitants per year, which means 500 patients per year in the USA [7]. Post-mortem evaluation of the presence of agents responsible for mucormycosis shows that mucormycosis is ten- to 50-fold less frequent than candidiasis or aspergillosis, and that it appears in one to five cases per 10 000 autopsies [8–10]. In

patients undergoing allogenic bone marrow transplantation, the incidence may be 2–3% [11,12].

The main risk-factors for the development of mucormycosis are ketoacidosis (diabetic or other), iatrogenic immunosuppression, especially when associated with neutropenia and graft vs. host disease in haematological patients, use of corticosteroids or deferoxamine, disruption of mucocutaneous barriers by catheters and other devices, and even exposure to bandages contaminated by these fungi [13–19].

Currently, one of the most controversial issues is the spectacular increase in the number of cases of mucormycosis in institutions that care for haemato-oncological patients [12,15,16,20–27]. This increase has generally taken place in patients and units where broad-spectrum antifungal prophylaxis, especially voriconazole, is used against *Aspergillus* [28–30]. A recent study by Kontoyiannis *et al*. [31] describes 27 patients from whom mucormycosis was retrospectively collected and compared with a group of 54 patients diagnosed with invasive aspergillosis during the same period, and with another group of 54 patients with the same features who did not suffer from invasive fungal diseases. Those patients with mucormycosis yielded isolates of Mucorales with different genotypes. All clinical isolates were voriconazole-resistant, and previous prophylaxis with voriconazole was an independent predictor of mucormycosis, as were diabetes mellitus and malnutrition [31]. Mucormycosis was the second most common invasive mycosis during the study period and occurred mainly in the lungs (59%) and sinuses (41%).

PATHOGENESIS

Mucorales invade deep tissues via inhalation of airborne spores, percutaneous inoculation or ingestion [1]. They colonise a high number of patients but do not necessarily cause invasion.

Once the spores have penetrated the lungs or subcutaneous tissues, they are met by the first line of defence, mononuclear and polynuclear phagocytes. The phagocytes of the healthy host are able to kill the spores of Mucorales by generating oxidative metabolites and defensins (cationic peptides) [32–34]. Severely immunocompromised neutropenic patients and those with phagocyte dysfunction (e.g., hyperglycaemia) are at greater risk of mucormycosis. Ketoacidosis decreases the movement of these phagocytes towards the source of the infection and their capacity for lysis by oxidative and non-oxidative mechanisms [35,36].

Another risk-factor for mucormycosis is the presence of high concentrations of iron in serum. Patients treated with deferoxamine have a high incidence of mucormycosis, probably because Mucorales use this chelant as a siderophore to obtain more iron [37]. It is well-known that administering iron or deferoxamine to animals infected with Mucorales reduces survival [38–40]. The increased risk of mucormycosis in patients with ketoacidosis may also be due to the release of iron bound to proteins [2,41].

If the spores escape phagocytosis, they can invade vessels, partly by efficacious adherence to endothelial cells, an ability that *Rhizopus oryzae* maintains even when the fungus is not viable [42].

CLINICAL MANIFESTATIONS

As previously mentioned, mucormycosis occurs mainly in those patients with diabetes mellitus and ketoacidosis, in patients with haematological malignancies [11,13,43–46], especially neutropenia [13,47] or graft vs. host disease, in solid-organ transplant patients [11,19,20,48–63] and in patients receiving high doses of corticosteroids [45]. Treatment with deferoxamine in patients with iron and aluminium overload has been associated with mucormycosis, although the introduction of erythropoietin has significantly decreased the use of deferoxamine, and therefore this factor is becoming progressively less frequent in current cases of mucormycosis [1,11,37,40,64–82]. Mucormycosis is very infrequent in immunocompetent patients, those without risk-factors, HIV-infected patients, intravenous drug users and patients with solid-organ tumors [33,37,41,83–125].

Finally, mucormycosis may occur after traumatic inoculation, especially in those cases where the inoculation is accompanied by contamination with water and soil. Mortality in these circumstances fluctuates between 38% and 80% [101,126–147].

Mucormycosis (Table 2) manifests most commonly in the sinuses (39%), lungs (24%), skin (19%), brain (9%), and gastrointestinal tract (7%), in the form of disseminated disease (6%), and

Table 2. Clinical manifestations of mucormycosis

Clinical manifestation	Underlying condition	References
Rhino-cerebral	Diabetes, ketoacidosis	[91,104,149–153]
Pulmonary	Neutropenia, corticosteroid therapy	[91,154,155]
Cutaneous	Trauma, diabetes	[18,91,156–159]
Gastrointestinal	Malnutrition	[91,160]
Disseminated disease	Deferoxamine, neutropenia, corticosteroids	[71,75–77,91,161]
Other (central nervous system, endocarditis, etc.)	Various	[91,162]

in other sites (6%) [91]. With the exception of rhino-cerebral and cutaneous mucormycosis, the clinical diagnosis of mucormycosis is difficult, and is often made at a late stage of the disease or post-mortem [148].

RHINO-CEREBRAL MUCORMYCOSIS

Rhino-cerebral mucormycosis, which should be termed rhino-sinus mucormycosis, is involved in between 33% and 50% of all cases of mucormycosis. The most frequent underlying conditions associated with this clinical manifestation are uncontrolled diabetes mellitus [1,2,104,150,151, 163–167] and leukaemia [168–172]. It is rare in solid-organ or haematopoietic stem-cell recipients [46,48,50,51,57,166,173–180], and occasionally occurs in patients with HIV infection [108,112,113,117,183] or other conditions [64, 72,73,181,182]. When a healthy patient is infected after facial trauma, *Apophysomyces elegans* should be considered as the first presumptive aetiological agent [83,126,127,132,135,136,144,146,184–187].

Clinical manifestations may start with necrosis of the palate or sinuses, which may progress towards the orbit before reaching intra-cranial structures [188,189]. The most frequent symptoms include fever, obnubilation, amaurosis, proptosis, epistaxis, facial paralysis and signs of invasion of the trigeminal nerve. Thrombosis of the cavernous sinuses and cranial invasion may be consequences of unresolved rhino-sinus mucormycosis.

Black sores on the palate or nasal mucosa are very suggestive of mucormycosis in the appropriate clinical context, although they may not be present in 50% of cases [190,191].

Species of the *Rhizopus* genus are the principal causes of these clinical manifestations [190]. Despite the rapid course of the disease, some forms may take weeks or months to develop [192–199].

The rate of mortality of rhino-orbito-cerebral mucormycosis is still very high and ranges from 30% to 69% [1,151,180]. Indicators of poor prognosis include a delay in treatment of more than 6 days, evidence of intra-cranial invasion, bilateral involvement, invasion of the palate, and the presence of haematological malignancies [180,200].

RESPIRATORY MANIFESTATIONS

Invasion of the lung is the second most common clinical manifestation and follows the inhalation of spores. The most frequent predisposing underlying condition has been considered to be haematological malignancy with neutropenia, although recent studies suggest that diabetes mellitus is the most frequent underlying condition [2,148,155, 188,201–204].

It is thus not easy to differentiate between mucormycosis and invasive aspergillosis. Manifestations are non-specific and include fever, haemoptysis and pleural pain. Mucormycosis usually occurs in the at-risk population alongside other common diseases, e.g., cytomegalovirus infection, bacterial infection or even other fungal diseases [202,203,205–207]. Endobronchial or tracheal lesions are common [197,208–215], and vascular involvement of great vessels may be a cause of fatal haemoptysis [216–224]. Symptoms may appear after near-drowning episodes [225], and the differential diagnosis of necrotising pneumonia or lung abscesses should be considered [204].

The radiological presentation of mucormycosis is similar to that of invasive aspergillosis, and both tend to show vascular invasion and thrombosis, followed by tissue necrosis. This

presentation includes cuneiform pulmonary infiltrates, pulmonary nodules and cavitated lesions, including the 'halo' sign [226,227].

The rate of mortality associated with pulmonary mucormycosis is high, and may be over 60%. The rate is higher among patients who do not receive appropriate treatment (systemic antifungal treatment combined with surgical resection and control of the underlying disease).

CENTRAL NERVOUS SYSTEM INVOLVEMENT

Mucormycosis of the central nervous system may be part of the progression of the disease from a rhino-orbital route or a clinical manifestation limited to the central nervous system [51,104,164,228,229]. Intravenous drug users have a particular predisposition to mucormycosis limited to the central nervous system [122,183,230–235], although this manifestation has proven to be anecdotal among immunocompetent patients [85]. The involvement of basal lymph nodes and the presence of lesions on magnetic resonance imaging scans are usual [231]. Non-specific signs of meningitis may be found in cerebrospinal fluid, although the culture yield is extremely low [193,236–238]. Optimal therapy combines medicine and surgery, although a patient has improved with medical treatment only [183].

CUTANEOUS INVOLVEMENT

The number of cases of cutaneous and soft tissue mucormycosis has increased during the last few years. This condition can occur on problem-free skin or follow the rupture of barriers, e.g., through surgery, trauma [147,239–244] or burns [245–250]. Sometimes, the infection begins at catheter insertion sites [19,156,159,251,252] or even after insect bites [156]. It has also been described after the use of contaminated dressings [253] and intramuscular injections [254].

Most patients with cutaneous mucormycosis have underlying conditions such as diabetes mellitus, solid-organ transplant and leukaemia, although this clinical manifestation is more common in patients with no known underlying diseases [255–257]. In one case review [156], Adam *et al*. observed that only 26% of patients with cutaneous mucormycosis had diabetes mellitus.

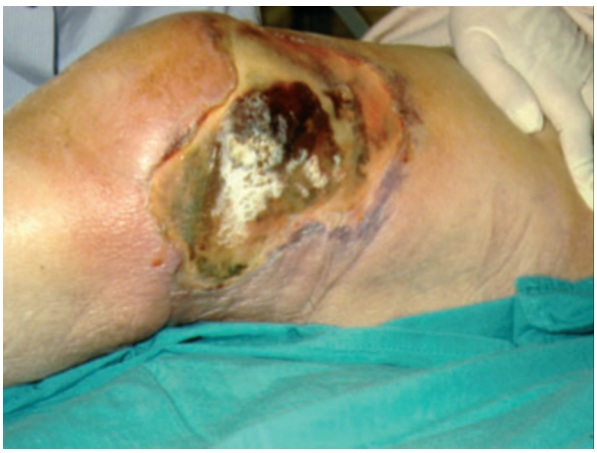

Fig. 3. Clinical manifestations of cutaneous mucormycocis.

The clinical manifestations of cutaneous mucormycosis are varied, and range from pustules or vesicles to wounds with wide necrotic zones (Fig. 3). In their early stages, lesions may be similar to those present in ecthyma gangrenosum. In extensive lesions, a cotton-like growth may be observed over the surface of the tissues, a clinical sign known as 'hairy pus'. Rapid diagnosis of cutaneous mucormycosis may explain the lower rate of associated mortality.

OTHER CLINICAL MANIFESTATIONS

Mucormycosis can involve any part of the digestive tract [59,160,258–277], with a mortality rate of 98% according to a published series of 25 accumulated cases [59].

Mucormycosis may be the cause of endocarditis in natural [162,278–280] or prosthetic valves [281] and has been reported to cause invasion and obstruction of the great vessels [162]. The clinical manifestations are extremely rare and the rate of mortality is very high [58,281–283].

The agents responsible for mucormycosis can affect the kidneys and, in these cases, nephrectomy is an essential part of treatment [56,109,284–288].

Osteomyelitis is another rare form of mucormycosis, and bone lesions are usually adjacent to other forms of mucormycosis (Fig. 4). It has been described at the base of the cranium [289], in the bones of the feet and hands [290–292], and in the humerus [293], tibia [294], femur [295] and vertebrae [296]. Mucormycosis is an extremely rare form of joint infection [297].

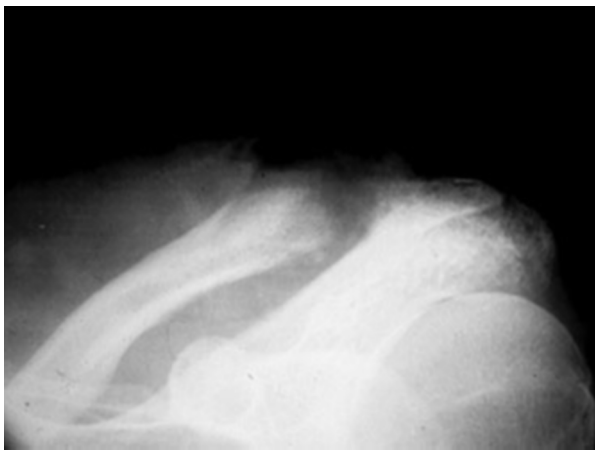

Fig. 4. Osteomyelitis, a rare form of mucormycosis.

Some cases of peritoneal mucormycosis have been described in patients undergoing continuous ambulatory peritoneal dialysis. These are usually complications of previous bacterial peritonitis [298–302].

DISSEMINATED DISEASE

Disseminated mucormycosis involves more than two contiguous organs. In 23–62% of the cases, it occurs in patients with haematological disease [13,47,64,86, 110,206,207,303–324] and, in most cases, the patient is deeply immunodepressed and suffering from neutropenia. Other risk-factors for dissemination are the use of corticosteroids, immunodepression after solid-organ transplant, chemotherapy and the use of deferoxamine. The rate of mortality in cases of disseminated mucormycosis is approximately 100% [1,155, 322,324].

DIAGNOSIS

The diagnosis of mucormycosis is relatively easy in the case of rhino-orbital and mucocutaneous involvement. Nevertheless, when deep tissues are invaded (e.g., in pulmonary mucormycosis), samples, and therefore a correct diagnosis, are more difficult to obtain. In patients suffering from haematological disease with pulmonary manifestations, an ante-mortem diagnosis can be made in less than 50% of cases [11,13,47,324].

Tests using cultures of clinical samples have limited sensitivity, and there are many reports of negative culture results both ante-mortem and post-mortem. This appears to be due to aggressive processing of the specimen before plating, especially when the samples are biopsy specimens, which should be cut into small fragments before plating. Tests using sputum have sensitivity values below 25% in pulmonary forms, and its specificity remains unknown, although it is generally believed to be low.

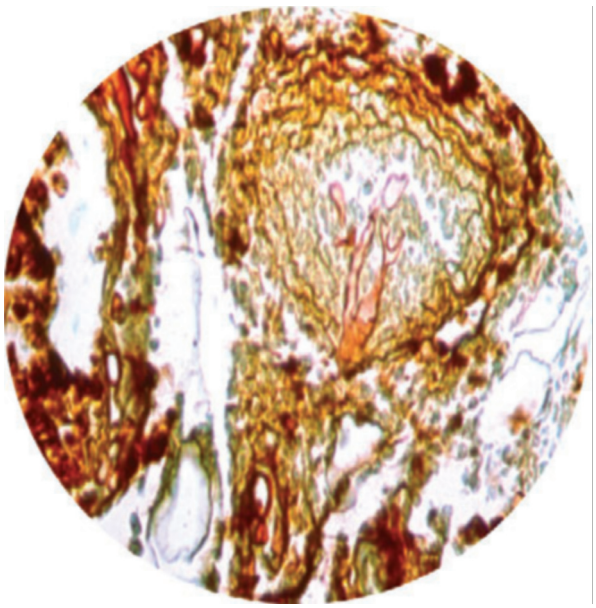

Fig. 5. Histological invasions of vessels, by wide, non-septate hyphae.

The presence of wide, non-septate hyphae in culture or on slides should always be interpreted with care, as they may represent colonisation. Thus, confirmation of the clinical form also requires the combination of symptoms compatible with histological invasion of tissues. Histopathological testing does not provide the genus and species, and should therefore be complemented with culture. Histological invasion, particularly of vessels, by wide, non-septate hyphae branched at right angles is diagnostic in an appropriate clinical context (Fig. 5). The probable diagnosis of mucormycosis requires the combination of various clinical data and the isolation in culture of the fungus from clinical samples.

Diagnosis by imaging is also difficult. In cases of rhino-orbital lesions, simple radiology and computed tomography scans usually show invasion of the sinuses, displacement of the orbit and invasion of the surrounding bone structures. When intra-cranial structures are affected, magnetic resonance imaging is the technique of

choice. Pulmonary mucormycosis causes lesions that may be non-specific and cannot be differentiated from those of invasive aspergillosis. Chamilos *et al.* [23] demonstrated that the presence of multifocal pulmonary sinusitis that progresses during anti-*Aspergillus* therapy suggests mucormycosis. Advances in molecular biology would greatly improve diagnostic capability in this area.

TREATMENT

The treatment of mucormycosis requires a rapid diagnosis, correction of predisposing factors, surgical resection, debridement and appropriate antifungal therapy.

As mentioned above, limited diagnostic tools mean that, in some studies, 50% of cases are diagnosed only post-mortem [4,9,325]. Therefore, physicians should be highly suspicious except when classic cutaneous or rhino-cerebral forms are involved. Furthermore, a delay in diagnosis means a worse prognosis for the disease [149].

Predisposing factors that could be addressed include diabetic ketoacidosis and the suppression of corticosteroids and deferoxamine.

Rapid and complete surgery, if possible, is the best treatment for mucormycosis. In fact, partial resection of necrotic tissue is better than none at all, although this is easier in the cutaneous and rhino-cerebral forms than in visceral forms. Very extended forms, particularly pulmonary and disseminated disease in neutropenic patients, are impossible to operate on in many cases [18,149,152].

Surgery combined with the use of antifungal drugs is always better than antifungal therapy alone [13,155,284,326–328].

One of the main difficulties in studying treatment of mucormycosis is the lack of large clinical trials. This may be due to the rarity of the disease, the high cost involved, the difficulty in developing multicentre studies, and the presence of variables, e.g., surgery, that would interfere with the interpretation of results. The choice of optimal antifungal therapy depends on the results of antifungal susceptibility testing studies, the results of studies in animal models, and the anecdotal experience gained from cases in humans.

Current data, although indirect, point to high-dose liposomal amphotericin B as the therapy of choice for this condition. Amphotericin B has shown variable activity *in vitro* against agents responsible for mucormycosis. Liposomal amphotericin B is better tolerated and has lower toxicity [153,171,180,198,329–333]. Liposomal amphotericin B at 5 mg/kg has not been shown to be inferior to higher doses.

Itraconazole, despite its in-vitro activity against Mucorales [334], and its success in a few clinical cases [52,335], is considered an inappropriate choice, and there is evidence of its failure in patients suffering from mucormycosis [15,153,307,336,337].

Voriconazole is not active *in vitro* against Mucorales [334] and failed when used *in vivo* [28,29].

Posaconazole and ravuconazole have good activity *in vitro* [334,338–340] and, in animal models, posaconazole has proven to be superior to itraconazole but less effective than amphotericin B deoxycholate [307,338]. Recent studies indicate that compassionate use of posaconazole is effective in clinical failures with amphotericin B and other treatments [334,336,338,340–343]. Currently, it is the most promising therapeutic alternative to amphotericin B.

Caspofungin has poor in-vitro activity against the agents responsible for mucormycosis, but an in-vitro/in-vivo correlation has not been well established. Caspofungin proved to be active *in vitro* by inhibiting the $(1 \rightarrow 3)$-β-D-glucan synthetase of *Rhizopus oryzae*, and in an experimental model of disseminated mucormycosis caused by this microorganism, low-dose caspofungin improved the survival of mice with mucormycosis induced by diabetic ketoacidosis. Some authors consider that further studies should be done to determine the potential role of caspofungin in mucormycosis [344], as there may be a synergy between caspofungin and amphotericin B lipid complex [331].

In an experimental murine model of disseminated mucormycosis, caused by *Rhizopus oryzae*, amphotericin B lipid complex was combined with caspofungin. The combination led to a higher rate of survival than with each drug used separately, although it did not reduce the fungal burden in tissue and was no more effective as prophylaxis [331]. Overall, clinical experience with caspofungin in mucormycosis is very limited and, currently, there is not enough evidence to recommend its use in the treatment of cases of mucormycosis.

Other echinocandins, e.g., micafungin, have shown good results in isolated cases of mucormycosis [26].

Other therapeutic alternatives include the use of iron chelants other than deferoxamine, and hyperbaric oxygen (especially in patients with rhino-cerebral forms), although the efficacy of both alternatives must be demonstrated in clinical trials, which are difficult to perform at present [345–348]. Cytokines such as gamma interferon or granulocyte–macrophage colony-stimulating factor have also been used to treat mucormycosis [349,350].

OUTCOME

The overall rate of mortality of mucormycosis is approximately 40%, but this rate depends on the clinical presentation of the disease, the underlying disease, surgery, and the extent of the infection [18,151,188,351].

Survival rates vary according to the focus of the infection: cutaneous isolated, 90%; sinusitis without cerebral involvement, 87%; rhino-cerebral manifestation, 45%; pulmonary forms, 36%; focal cerebral manifestation, 33%; disseminated disease, 16%; and gastrointestinal involvement, 10%.

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