

Entry

Mucormycosis—Emerging Fungal Threats

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Definition: Mucormycosis is an opportunistic fungal infection due to organisms of the *Zygomycetes* class and the order of *Mucorales* that can cause various types of infections. In recent years, an increasing phenomenon has been observed—invasive fungal infections especially in the healthcare setting. Among immunocompromised patients, an important clinical emergency could be represented by mucormycosis. The epidemiology of mucormycosis has shown an alarming trend and its incidence is rising globally. Four elements are fundamental for a successful treatment: rapid diagnosis, reduction of predisposing factors (if possible), surgical debridement of infected tissues, and appropriate antifungal therapy.

Keywords: emerging fungal infections; mucormycosis; emerging infections; *Mucorales*



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1. An Overview on Emerging Infectious Diseases

The end of the 1970s was supposed to be the “end of infectious diseases”. This optimism derived from the success of the fight against infectious diseases due to the development of hygiene, environmental hygiene, the advent of anti-infective drugs, and vaccine—vaccination programs including those against smallpox. With the identification of new infectious agents (*Legionella*, rotavirus, Ebola virus, Hantaan virus, *Campylobacter*, prions, etc.), the emergence of acquired immunodeficiency syndrome (AIDS) and its global spread, as well as the progression of bacterial resistance to antibiotics, the “return of infectious diseases” was pronounced [1].

The American Centers for Disease Control and Prevention developed a strategic plan to combat emerging infections in 1994 based on surveillance, alert and response, applied research, prevention and control, and strengthening public health facilities. The World Health Organization (WHO) therefore launched a comprehensive plan based on the same principles [2].

As reported by Barreto et al., a communicable disease, also known as an infectious disease, could be defined as “an illness caused by a specific infectious agent or its toxic product that results from transmission of that agent or its products from an infected person, animal, or reservoir to a susceptible host, either directly or indirectly through an intermediate plant or animal host, vector or inanimate environment” [3].

Infectious diseases can occur as both endemic (diseases constantly present in a population or in a certain geographical area) and epidemic (sudden increase in the number of cases, higher than expected). When an epidemic is geographically very extensive and affects many individuals of the population, it is called a pandemic. Epidemics and pandemics have always been conceived in the collective imagination as a dangerous threat from which it is difficult to escape in the event of contagion [3].

Occasional and exceptional outbreaks of infectious diseases have had deep and durable effects on societies throughout history. For example, the Athenian plague is a historically

documented event that occurred in 430–26 BC during the Peloponnesian War, fought between the city-states of Athens and Sparta. Thucydides provided a historic account of the Athenian plague and survived the plague, describing it in his History of the Peloponnesian War [4]. However, we could also note the Manzoni plague (1629); the flu pandemic known as “Spanish” flu (1918); and, recently, AIDS (1980) [5], SARS (severe acute respiratory syndrome) (2003), and SARS-CoV 2 (2019) [6]. For centuries, humanity had to passively undergo these events until the definition of the theory of germs and the discovery of bacteria, with the identification of specific microorganisms responsible for various infectious diseases, which allowed for the subsequent discovery and development of vaccines and antibiotics. However, in recent years, despite the enormous progresses made in the biomedical field, microorganisms have continued to emerge and re-emerge and spread worldwide without any possible forecast [7].

As Reported by Van Doorn et al., emerging infectious diseases are defined as “those whose incidence in humans has increased within the past two decades or threatens to increase in the near future. Emergence may be due to the spread of a new agent, to the recognition of an infection that has been present in the population but has gone undetected, or to the realization that an established disease has an infectious origin” [8].

The causes of the emergence or re-emergence of microorganisms can be numerous.

Changes in the geographical footprint of pathogens or parasites could be determining factors associated with the emerging infections. This may be due to changes in the natural geographical ranges of animal hosts of zoonoses and vectors, and/or via the dispersal of pathogens in infected humans, animal reservoirs, or vectors [9].

Instead, “adaptive emergence” is the genetic change of a microorganism that results in a phenotype that is capable of invading a new ecosystem, particularly via jumping to a new host species, including humans [10].

In addition, all these factors can interact together and create the conditions for a microorganism to evolve, thus acquiring the ability to reach the host and to adapt and spread much more easily in humans. Depending on whether the microorganism is emerging or re-emerging, the possible causes and the prevention measures to be implemented may be different. Any infectious disease can become an emergency when it takes on an epidemic character or when it is perceived by the population as being dangerous [7,11].

The advent of new therapies has deeply changed the treatment of cancers and autoimmune diseases, but some of these therapies (especially immunomodulators) can be complicated by the onset of invasive fungal infections. For example, the Bruton tyrosine kinase inhibitor (ibrutinib) (to treat malignant B cell tumors) could be linked to severe infections due to *Aspergillus* and *Cryptococcus*, while cryptococcosis and histoplasmosis could be a complication of treatment with Sphingosine-1-phosphate receptor modulator fingolimod (used for multiple sclerosis) [12].

One of the most troubling changes in the epidemiology of invasive candidiasis is the emergence of *C. auris*, a potential multi-drug resistant and nosocomially transmitted organism. Since being described in Japan in 2009, *C. auris* has been reported in 32 countries on six continents [13].

As for invasive aspergillosis (IA), it has a high mortality percentage in immunocompromised patients. *A. fumigatus*, the most common species, is often highly susceptible to new triazole antifungals such as itraconazole, voriconazole, and posaconazole. However, various countries around the world have reported *A. fumigatus* resistant to azoles [14].

2. Nosocomial Fungal Infections

Healthcare and nosocomial environment has observed an increase in invasive fungal infections and, as a lot of risk factors could contribute to their increase, and their frequency is increasing, it is likely that the number of nosocomial fungal infections will increase in frequency in the next decades [15].

Beyond the emergence of antifungal resistance, the improvement of medical technologies (for example transplantation for organ failure, immunosuppression for autoimmunity,

and myeloablative and targeted therapies for cancer) has placed human populations at higher risk for invasive mycoses, and in resource-limited settings, the AIDS pandemic continues to be defined by life-threatening fungal diseases [16].

Immunosuppression is inversely related to fungi's ability to cause nosocomial infections [15].

Organisms such as *Mucorales*, *Fusarium*, and other molds (e.g., *Scedosporium*) are relatively less common, and are identified almost exclusively in the more severe immuno-compromised hosts and in hosts that are compromised for prolonged periods of time [15].

Reduced cell-mediated immunity may also predispose geriatric patients to nosocomial cryptosporidiosis [17].

C. auris, a recently identified new *Candida* species, is now considered a well-known health care-associated yeast that causes invasive infections with a high frequency of treatment failure [13].

In past years, other fungi (whose frequency is relatively rare) have been involved in health care-associated epidemics; among them, *Exserohilum rostratum*, *Sarocladium kiliense*, and *Saprochaete clavate* [13].

So, greater surveillance and use of advanced technologies is fundamental to rapidly detect the possible sources of these infections, and therefore to conduct an efficient epidemiological investigation and implement adequate control measures [13,18].

3. Mucormycosis—Introduction

In recent years, mucormycosis, a fungal infection caused by *Mucorales*, is becoming an interesting and alarming phenomenon [19], because of the increase in cases, the high mortality rates, and the lack of effective antifungal treatments. In the past, it was considered a rare infection and limited to patients with severe immune alterations (for example patients suffering from AIDS, diabetes, organ transplants, or other conditions associated with immunosuppression), but the progressive improvement in diagnostic techniques has revealed that numerous cases have also involved immunocompetent individuals.

Mucormycosis is an opportunistic fungal infection due to organisms of the *Zygomycetes* class and the order of *Mucorales* that can cause various types of infections. Several cases are characterized by the presence of underlying conditions that increase the hosts' predisposition to infection [20].

The species most frequently isolated from patients are *Apophysomyces* (*A. variabilis*), *Cunninghamella* (*C. bertholletiae*), *Lichtheimia* (*L. corymbifera* *L. raosa*), *Mucor* (*M. circinelloides*), *Rhizopus* (*R. arrhizus*, *R. microsporus*), *Rhizomucor* (*R. pusillus*), and *Saksenaea* (*S. vasiformis*) [20].

4. Mucormycosis—Frequency

Fungi belonging to the *Mucorales* order are distributed in six families, which can cause skin and deep infections.

Mucormycosis is a very serious fungal infection—a real clinical emergency—which occurs mainly in patients who are immunosuppressed or who have elevated serum iron.

Humans acquire the infection predominantly through the inhalation of sporangiospores, occasionally through the ingestion of contaminated food or traumatic inoculation [21,22].

In recent years, the epidemiology of mucormycosis has shown an alarming trend—especially in countries such as India and China, a rise in incidence especially among patients with uncontrolled diabetes mellitus has been observed [23].

Mucormycosis, in the past almost always acquired in the community and often in the context of diabetic ketoacidosis, has rapidly become a nosocomial infection in patients with cancer or undergoing organ or bone marrow transplantation (haematopoietic stem cell transplantation (HSCT)). In fact, in patients undergoing allogeneic bone marrow transplantation, the prevalence of mucormycosis is as much as 2–3%.

Overall, the most common underlying diseases of patients affected by mucormycosis are represented by steroid therapy (37%), followed by solid organ transplantation (24%), diabetes mellitus (22%), and malignancy (12%). The skin was the most common site

involved (57%), followed by gastrointestinal tract (15%), lungs (8%), sinuses and brain (4%) [23].

However, some outbreaks with an iatrogenic cause have also been described in the context of dressings or through the use of contaminated medical instruments [15], and a noticeable number of cases have been reported in patients without any underlying disease or risk factors [23].

During the COVID-19 pandemic, cases of mucormycosis have been described as a complication of the diseases, especially in patients with diabetes mellitus or in those who used glucocorticoids for COVID-19. The most common sites of involvement by mucormycosis was rhino–orbito–cerebral, pulmonary, gastric, and disseminated, with a high mortality rate [24].

5. Mucormycosis—Management

A multi modal approach should be used for the successful management of mucormycosis: this approach includes the elimination or reduction of the underlying predisposing factors (if possible), prompt administration of effective antifungal drugs, and complete eradication of all infected tissues and the use of various adjunctive therapies [25–27].

Four factors could be considered critical for successful treatment mucormycosis: rapid diagnosis, reversal of underlying predisposing factors, adequate surgical debridement, and appropriate antifungal therapy.

5.1. Diagnosis

Small focal lesions can often be treated and removed with a surgical approach, so early diagnosis is extremely important before they progress.

A clinical approach to diagnosis has a low sensitivity and specificity [28]; furthermore, the clinical manifestations of invasive aspergillosis and mucormycosis can be similar and both diseases affect similar populations of high-risk patients (cancer, transplants, etc.).

The demonstration of fungal hyphae with aspects typical for mucormycetes leads to a definitive diagnosis: they can be retrieved in biopsies of infected tissues, or in the bronchoalveolar lavage (BAL) in patients with pulmonary mucormycosis. Other fungi, including *Aspergillus*, *Fusarium*, or *Scedosporium*, may appear to be similar to *Mucorales* during biopsy. However, these molds usually have thinner septae that branch out at acute angles.

In order to make the right distinction between the presence of the fungus as a pathogen and the presence of fungus as culture contaminant, it is essential to use the histopathology as diagnostic tool and it is indispensable to define whether there is blood vessel invasion [29].

For a rapid presumptive diagnosis of mucormycosis, direct microscopy of KOH wet mounts can be used. Direct microscopy of the fresh material has a low cost, and is a useful method to rapidly provide a presumptive diagnosis and to define clear surgical margins for invasive fungal infection intraoperatively [30].

For identification to the genus and species level, but also to test the antifungal susceptibility, it is recommended to culture the specimens. The major concern about culture, however, is its low sensitivity, as it can be falsely negative in up to 50% of mucormycosis cases [31,32].

Molecular methods (PCR-based) require further clinical studies for their validation, but are useful tools to confirm the infection and identify the strains involved. In samples with the characteristic hyphae of *Mucorales* upon histopathological examination, the application of molecular methods confirms the diagnosis, and are therefore highly recommended [33]. Unfortunately, in some cases, the diagnosis is made post mortem.

5.2. Risk Factors

It has been widely reported that mucormycosis acquired in a nosocomial setting has been ascribed especially to iatrogenic immunosuppression. The myelodysplastic syndrome that could underline transplantation could be an additional risk factor, maybe because of

repeated blood transfusions and therefore iron overload, while the steroid-treated graft versus host disease, or the administration of anti-thymocyte globulin may also be further risks for mucormycosis.

Pulmonary mucormycosis most commonly occurs in leukemic patients undergoing chemotherapy or in patients undergoing HSCT. Conversely, soft tissue infections may occur in patients with altered skin barriers: they could be ascribed to traumatic impact with the ground, to skin maceration caused by a moist surface, or in nosocomial settings through direct access through intravenous catheters or subcutaneous injections. Cutaneous mucormycosis has been also described as a consequence of contaminated surgical dressings. In one case, cutaneous mucormycosis occurred because of contaminated tape used to secure an endotracheal tube in a ventilated patient [15].

The efficient correction and control of such predisposing problems is therefore essential to improve the survival and outcome. In particular, it is imperative to maintain close control of diabetes and to resolve any acidosis immediately. Hyperglycemia impairs chemotaxis and the oxidative and non-oxidative fungicidal mechanisms used by phagocytic cells—the main defensive mechanism against mucormycosis. In states of acidosis related to hyperglycemia, free iron becomes readily available in the serum [34]. Recent studies in fact reported a lower incidence of the disease in diabetic patients, and these findings are probably due to better glycemic control and to a decrease in diabetic ketoacidosis, and to the common usage of statins in patients with diabetes [35].

Dose interruption or the reduction of corticosteroids should be considered when diagnosing mucormycosis. As also shown by Hoang et al., patients on chronic corticosteroid therapy have a higher risk for pulmonary mucormycosis [34]. Corticosteroids, in fact, could alternate the migration, ingestion, and phagolysosome fusion of bronchoalveolar macrophages.

5.3. Surgery

Antifungal therapy only is often unable to completely control mucormycosis because of its often rapid progression. Furthermore, it frequently has insufficient penetration of anti-infective agents into the site of infection due to the multiple distinctive characteristics of the disease (the angioinvasion, thrombosis, tissue necrosis). Therefore, the antifungal agent may be ineffective *in vivo*, even if the *in vitro* test has shown a discrete susceptibility [15]. As suggested by Losee et al. [36], a high index of suspicion and a low threshold for wound biopsy must be maintained and, for an early diagnosis, chemotherapy and surgical debridement of grossly necrotic tissue must be performed at the earliest possible time. While, in case of delayed diagnosis and/or advanced or rapidly progressive disease, surgical debridement of all involved tissue, in addition to chemotherapy, is warranted.

Multani et al. conducted a study on pulmonary mucormycosis and observed no significant postoperative survival for the factors of age, primary disease, ASA status, extra-pulmonary dissemination, laterality, multilobar involvement, number of lesions, largest lesion size, platelet count, surgical approach, type of resection, or extent of resection. The only element that was able to significantly increase survival was the surgical resection [37].

5.4. Antifungal Therapy

In vivo and *in vitro* laboratory studies and some clinical studies have demonstrated the efficacy of amphotericin B (AMB) [38]. However, the optimal dosage of amphotericin B for the treatment of mucormycosis (as already occurs with many antifungal agents and mycoses) is still undetermined. Lipid formulations of amphotericin have a significantly lower toxicity on kidney function compared to amphotericin B deoxycholate, and can be safely administered at higher doses over a longer period of time.

The French Mycoses Study Group conducted a phase I–II prospective, multicenter, pilot trial on the efficacy and safety of high-dose (10 mg/kg/day) LAMB monotherapy (AmBizygo study) for the treatment of mucormycosis [39].

The historical controls instead received a standard dose of 5 mg/kg/day. In the study, after 12 weeks of treatment, no significant improvements in mortality and response rates were observed, while the higher dose of L-AMB was associated with increased nephrotoxicity and electrolyte derangements. However, especially when there is an involvement of the central nervous system or of the osteoarticular system (and in selected cases) dosages >5 mg/kg/day could be considered [26].

Chamilos et al. showed that delaying effective amphotericin B-based therapy in patients with hematological malignancies for >5 days resulted in an approximately two-fold increase in 12-week mortality (82.9% compared to 48.6% for those who started treatment immediately) [40].

There are no data about the use of posaconazole as a first line therapy, although posaconazole revealed an in vitro and in vivo activity against *Mucorales*. Posaconazole, therefore, could be used as a further therapeutic strategy for prophylaxis or for consolidation after induction treatment with lipid formulations of amphotericin. No studies have been conducted on the efficacy of posaconazole in mucormycosis treatment (both in intravenous or tablet formulations). Moreover, some mucormycosis cases have been described in patients undergoing posaconazole prophylaxis, despite satisfactory serum concentrations [41,42].

A study conducted on isavuconazole, instead, revealed its positive cost effectiveness if compared to amphotericin B during mucormycosis treatment: in fact, isavuconazole has a broad antifungal spectrum, linear pharmacokinetics, and a high oral bioavailability [43].

In vitro tests revealed a low activity of echinocandins against mucormycosis agents. Literature data suggest that echinocandins could be used as a second agent, especially in combination with a polyene, in severe cases of mucormycosis. In this context, further studies on the usefulness of echinocandins are needed [15,44].

In a recently published case report authors reported in an immunocompetent patient with extensive abdominal mucormycosis unresponsive to conventional therapy, the benefit of a treatment with nivolumab and interferon- γ [45].

5.5. Chelation Therapy

Iron availability is a critical factor in the growth of *Mucorales* [46]. As iron and its metabolism have a central role in the pathogenesis of mucormycosis, the possibility of using effective iron chelators as complementary antifungal therapy has been suggested. Deferoxamine acts as a siderophore to supply iron to the fungus, while deferasirox and deferiprone do not facilitate iron uptake by the fungi, apparently because they share higher-affinity constants for iron, so they deprive the fungi of iron, and hence its growth [47]. The study of M. N. Chitasombat et al. in 2018 [48] showed preliminary safety and tolerability data of adjunctive deferiprone (DEF) for the treatment of mucormycosis in conjunction with antifungals and surgery.

Deferasirox is a new orally available iron chelator that was recently approved by the US Food and Drug Administration (FDA) for the treatment of iron overload in transfusion-dependent anemias. Deferasirox was used in a patient with rhino-orbito-cerebral mucormycosis [49]: the patient was treated with an orally administered dose of deferasirox 15 mg/kg, which was stopped within 48 h of the first dose because of the significant and rapidly worsening renal function. However, authors suggest it may be beneficial for improving survival using a combined therapy based on iron chelators and effective antifungal drugs.

However, this aspect the debate is still open. In fact, Spellberg et al. in their study observed an excess mortality of patients treated with adjunctive deferasirox therapy, so they affirmed that deferasirox should not be recommended as part of a standard therapeutic regimen for the treatment of mucormycosis. They identified no evident toxicities, but the study involved a limited number of patients, so it was not possible to establish the safety of deferasirox therapy for mucormycosis. Therefore, they concluded that in absence of

further studies, it is better to use caution when administering deferasirox for patients with mucormycosis, even in a salvage setting [50].

6. Conclusions

Among the emerging invasive fungal infections, Mucormycosis are those that require a high level of clinical expertise for a correct diagnosis, and therefore to improve patients' survival. Sometimes and if available, several types of diagnostic advanced tests should be used to reach the correct diagnosis. First-line therapy is amphotericin B combined with surgical debridement; other antifungal drugs could also be used. The management and control of underlying conditions is an essential element to prevent these infections and to improve their therapy.

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