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"Mucormycosis" The Emerging Global Threat - A Complete Review

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ABSTRACT

Mucormycosis is a life-threatening invasive fungal infection that affects people who are immunocompromised (haematological malignancies, solid organ transplantation, diabetes mellitus). Pulmonary, rhinocerebral, cutaneous, and disseminated infections are the most common. Controlling mucormycosis requires reversing the underlying problems. Treatment for mucormycosis also includes quick and vigorous surgery. Extensive surgical debridement of necrotic tissues is required. Finally, an antifungal treatment is required. High-dose liposomal amphotericin B (5 mg/kg/day) is the first-line treatment for mucormycosis. Antifungal chemotherapy has no set length; instead, it is determined by the remission of all related symptoms and results (usually 6-8 weeks). Posaconazole maintenance therapy/secondary prophylaxis should be recommended in patients who have a persistently weakened immune system.

Keywords: Mucormycosis, Diabetes mellitus, Liposomal Amphotericin B

INTRODUCTION

Mucormycosis are life-threatening fungal infections that primarily affect haematological, solid organ transplant, and diabetic patients, although they can also harm immunocompetent patients after a trauma or burn. [1] There has been reports of nosocomial or communal outbreaks. [2] Mucormycetes are classified as Mucorales in the Mucoromycotina subphylum.[3] Pulmonary, rhino-cerebral, cutaneous, and eventually disseminated fungal infections are the most common. The therapy of these infections is based on a triptych that includes stringent control of risk variables, particularly balancing an underlying diabetes, early surgical management with necrotic tissue excision, and finally, medication management. The number of people at risk for this lethal illness is significantly increasing due to the rising prevalence of diabetes mellitus, cancer, and organ transplantation in the aging US population. [4] Despite disfiguring surgical debridement and adjunct antifungal therapy, the overall mortality rate for mucormycosis is still over 50%, and it approaches 100% among patients with widespread disease or chronic neutropenia .[5,6]

CLINICAL FEATURES

The clinical manifestations of mucormycosis are frequently linked to underlying diseases. Those with diabetes mellitus are more likely to develop rhino-cerebral mucormycosis, whereas patients with haematological malignancies are more likely to develop pulmonary mucormycosis.[7] In patients with pulmonary mucormycosis, radiological abnormalities are linked to immunological status.[8] Recently, there have been diagnoses in the gastrointestinal system, which is unusual.

- Rhinocerebral mucormycosis is initiated with inhalation of spores into the paranasal sinuses and the invasion of blood vessels in the tissue. The infection starts with nasal congestion or

discharge, though it may progress to facial numbness, blurry vision, nasal discharge, nasofrontal headache, ocular pain, fever, diplopia, and chemosis. Intranasal lesions characteristically have painless ulcerations with exudate and necrotic tissue, and usually progress rapidly over days. In an immunocompromised patient with prolonged nasal symptoms, one should maintain a low threshold to obtain a biopsy to rule out mucormycosis (often termed "invasive fungal sinusitis - IFS).[9]

- Pulmonary mucormycosis consists of the development of bilateral pneumonia, which is rapidly progressive and the result of the inhalation of infectious material. The most common clinical features are fever, hemoptysis, dyspnea, and cough. This clinical form is seen more frequently in patients with hematological diseases. This pulmonary condition can present as bronchitis, bronchopneumonia, and even pulmonary embolism. The infection can spread to contiguous tissues, such the mediastinum and heart, though it may also lead to cavitary lesions that can mimic tuberculosis or more benign allergic fungal disease. [10]
- Cutaneous mucormycosis presents in both primary and secondary disease. In primary disease, the skin infection results from direct inoculation and in secondary form, by dissemination from other locations. The primary form often occurs in patients with burns and traumatic skin wounds, usually appears as a single and indurated area of cellulitis that progresses a necrotic lesion, other forms of manifesting are abscesses, skin swelling, and necrosis.[11]
- Gastrointestinal form occurs via the ingestion of contaminated food, though the use of contaminated herbal medicines has been linked to gastrointestinal disease development. There may be nausea, vomiting, ulceration, and thrombosis of the gastric, esophageal and intestinal mucosa, manifested by diarrhea, hematemesis, and melena. Perforation and peritonitis can result from necrotic ulcers. Also, the presence of bowel infarctions and hemorrhagic shock lead to poor prognosis. Gastrointestinal symptoms are rare in all but the most severely immunocompromised (leukemia patients, intestinal transplant patients, etc.), owing to a large amount of immune tissue in the GI tract.[12]

PATHOPHYSIOLOGY

HOST DEFENSE MECHANISM

Both mononuclear and polymorphonuclear phagocytes of normal hosts kill Mucorales by the generation of oxidative metabolites and the cationic peptides defensins [13, 14]. Clinical evidence demonstrates that these phagocytes are the major host defense mechanism against mucormycosis. For example, neutropenic patients are at increased risk of developing mucormycosis. Furthermore, patients with dysfunctional phagocytes are also at higher risk for developing mucormycosis. Hyperglycemia and acidosis are known to impair the ability of phagocytes to move toward and kill the organisms by both oxidative and nonoxidative mechanisms.[15] Additionally, corticosteroid treatment affects the ability of mouse bronchoalveolar macrophages to prevent germination of the spores in vitro or after in vivo infection induced by intranasal inoculation. The exact mechanisms by which ketoacidosis, diabetes, or steroids impair the function of these phagocytes remain unknown.

IRON UPTAKE AND MUCORMYCOSIS

Mucorales also include virulence factors, which allow the organism to cause disease in addition to host characteristics that predispose people to mucormycosis. The ability to obtain iron from the host is one such characteristic. Iron is required for cell growth and development, and it plays a role in a number of important cell activities.[16] As a result, viruses that are

successful in getting iron from their hosts employ a variety of methods.

Recent research shows that the amount of accessible, unbound iron in the blood plays a key role in predisposing DKA patients to mucormycosis .[17,18] Iron is coupled to host carrier proteins such transferrin, ferritin, and lactoferrin in mammalian hosts. This sequestration prevents free iron from being harmful. Because R. oryzae grows poorly in normal serum unless exogenous iron is supplied, this strategy of reducing iron availability is also a major universal host defence mechanism against microorganisms in general, and against Mucorales in particular .[17,18] The clinical fact that patients with DKA are particularly prone to mucormycosis supports the theory that iron absorption plays a role in the disease's aetiology. DKA patients have high levels of free iron in their blood, which favours R. oryzae development at acidic pH (7.3–6.88) but not at alkaline pH (7.78–8.38). Animal research demonstrated that iron chelators like deferiprone and deferasirox, which Mucorales do not use as xenosiderophores, protected mice with DKA from R. oryzae infection. However, not all Mucorales are susceptible to iron chelators in the same way.[19,20]

DIAGNOSIS

Mucormycosis is difficult to diagnose, and therapy should begin as soon as possible to reduce mortality. Tissue biopsies for histopathology and culture should be obtained at all costs. Unfortunately, due to severe thrombocytopenia, this is typically problematic in individuals with hematologic malignancies. If a biopsy is not possible, all available specimens, such as sputum, should be examined directly and cultured. Sinus biopsies are required in cases of sinusitis.

- Endoscopy of the ear, nose, and throat (ENT) should always be performed and repeated to assess the response to treatment. If sputum smear analysis is negative in the event of pulmonary involvement, Broncho-alveolar lavage or pulmonary biopsies (endoscopic, CT-guided, or surgical) should be performed, based on the radiological findings acquired by CT scans.
- Endoscopic assessment and biopsy of the sinuses to test for tissue necrosis and retrieve tissue samples is the initial intervention in the suspicion of rhino cerebral mucormycosis; the presence of distinctive hyphae establishes a presumptive diagnosis.
- A CT chest scan should be performed on patients with immunosuppression and respiratory symptoms to rule out pulmonary mucormycosis. Because the infection has a similar appearance to pneumonia, diagnosing it can be difficult. Pleural effusion, nodules, consolidation, and ground-glass infiltrates are all common radiologic findings in the chest. Broad no septate hyphae can be seen in Broncho alveolar lavage.
- A CT scan to evaluate for colitis is required if there is a risk for gastrointestinal mucormycosis (abdominal discomfort, gastrointestinal bleeding). Colitis should be studied further by endoscopy with biopsy once it has been diagnosed. A tentative diagnosis might be made based on the presence of distinctive hyphae in the biopsy. [21,22]

PROGNOSIS

The prognosis is determined on the timing of therapeutic intervention as well as the severity of the patient's underlying immunodeficiency, with mortality rates ranging from 25% to 87 percent depending on the infection site.

Disseminated infection, renal injury, central nervous system disease, and inadequate response to medical treatment are all severe and poor prognostic markers. The ability to return to a normal immunological status is the most important prognostic factor. If this isn't achievable, the outlook is often bleak. Prognosis improves

if immunocompetence can be restored, even if only briefly. [23]

TREATMENT

The first-line recommended antifungal agent is liposomal Amb (L-Amb) or Amb lipid complex (ABLC). [24] Amphotericin B (Amb) and its lipid formulations and posaconazole were the only antifungal drugs avail*able with in vitro activity against mucorales* .[25,26] The antifungal armamentarium recently enlarged with the development of isavuconazole.

ECMM/ESCMID and ECIL-6 guidelines recommend the use of L-Amb with a daily dosage of at least 5 mg/kg/day for mucormycosis, and dosages at 10 mg/kg/day are strongly supported by ECMM/ESCMID for cerebral infections.[25] Moreover, because of better diffusion, L-Amb should be favoured in central nervous system infections.

The duration of the first-line antifungal treatment is still a matter of debate and should be determined on an individual basis and adjusted based on the underlying condition. Some authors proposed a lipid Amb treatment for at least three weeks, and, when there is clinical and radiological improvement, a consolidation by posaconazole can be started. [26] However, it could possibly be guided by negative PCR and therefore shortened for some patients.

In the VITAL study, isavuconazole was well tolerated and toxic effects were an uncommon cause of discontinuation. The place of isavuconazole has not yet been specified in the most recent guidelines [27]. Finally, a cost-effectiveness study demonstrated the positive economic impact of the use of isavuconazole compared to Amb in the treatment of mucormycosis [28]

Posaconazole has been shown to have *in vitro* and *in vivo* activity against *mucorales*, but there are no data for the use of first-line posaconazole therapy. Posaconazole, therefore, finds its place in the therapeutic armamentarium for prophylaxis or consolidation after induction treatment with L-Amb. No study on the efficacy of posaconazole intravenous or tablet formulations in mucormycosis treatment were conducted. Finally, mucormycosis cases have been reported in patients undergoing posaconazole prophylaxis despite satisfactory serum concentrations. [29]

However, it seems important to note that there are no current validated MIC breakpoints for any of the available antifungals and thus the determination of susceptibility categories is not possible for the agents of mucormycosis.

Management	**Comments**
Management includes antifungal therapy, surgery and control of underlying conditions	Multidisciplinary approach is required
Antifungal therapy Amphotericin B deoxycholate Liposomal Amphotericin B Amphotericin B lipid complex Amphotericin B colloidal dispersion Posaconazole Combination therapy Control of underlying conditions	 Daily dose 5mg/kg Liposomal Amphotericin B should be preferred in CN infection and /or renal failure No data to support its use as first line treatment. Alternative when Amphotericin B formulations are absolutely contraindicated Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation or tapering of steroids, reduction of immunosuppressive therapy
Surgery Rhino- orbito –cerebral infection Soft tissue infection Localized primary lesions Disseminated infection	Surgery should be considered on a case by case basis using a multidisciplinary approach

CONCLUSION

Mucormycosis is an uncommon but rapidly spreading fungus that has a high fatality rate. The majority of known mucormycosis epidemiology researches are retrospective and limited. There are few prospective, population-wide investigations of it in the literature. The investigations that

were available were mainly conducted at institutions with specialised populations at risk for mucormycosis (patients with HM and recipients of transplants). Although the generalizability of this result is debatable, mucormycosis appears to be on the rise among leukemic patients and stem cell transplant recipients who are persistently exposed to Aspergillus-active drugs. . Despite the global diabetes epidemic, the incidence of mucormycosis among diabetics appears to be declining. Uncontrolled diabetes mellitus and trauma, on the other hand, are the most common risk factors for mucormycosis in underdeveloped nations. For a more accurate assessment of the infection, more representative data on specific patient groups (e.g., leukemic patients, transplant recipients, diabetics) is required. To quantify the burden of mucormycosis, well-organized global registries are required.

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