MUCORMYCOSIS: A SYSTEMATIC REVIEW

Shubham Sharma*, Jobanpreet Kaur, Ravi Kumar, Varun Kumar, Sonia Kaur and Khushmeen Kaur

G.H.G. Khalsa College of Pharmacy, Gurusar Sadhar, Ludhiana 141104.

ABSTRACT
Mucormycosis refers to any fungal infection produced by Mucorales fungus. Mucormycetes are classified as order Mucorales in the Mucoromycotina subphylum. Mucormycosis rhinocerebral (sinus and brain) is a sinus infection that can migrate to the brain. Mucormycosis is the most common in patients who have uncontrolled diabetes or who have undergone a kidney transplant. Hyphae developing in and around blood vessels is a common symptom of the illness, which can be life-threatening in diabetics or those who are severely immunocompromised. On the other hand, Zygomycota has been determined to be polyphyletic and is not included in the contemporary fungal classification. The disease is also known as a black fungus. Antifungal medications are used in conjunction with surgical intervention in the treatment of fungal infections. Isavuconazole, the sole novel drug with action against Mucorales, was recently FDA authorized to treat invasive aspergillosis and invasive mucormycosis. Mucormycosis epidemiology has changed in recent years due to an increase in prevalence, new causative agents, and a vulnerable population. The growth has been noticed throughout the world, but it is the most noticeable on the Asian continent. In Asia, diabetes mellitus still outnumbers all other risk factors, although post-tuberculosis and chronic renal failure are emerging as new risk categories. This review highlights the overview of Mucormycosis with treatment.

KEYWORDS: Mucormycosis, Zygomycosis, Pathogenesis, Rhinocerebral, Diabetes mellitus, Aspergillosis.

INTRODUCTION
Mucormycosis is an angiopathic illness characterized by tissue necrosis and infarction. It is the third most common invasive mycosis after candidiasis and aspergillosis, which is caused
by a fungus of the Zygomycetes class. Mucorales and Entomophthorales are the two orders that make up the Zygomycetes class. Angioinvasive fungal infections are frequently caused by fungi belonging to the class Zygomycetes and the order Mucorales, especially in individuals with underlying risk factors. Molds enter the human body through the respiratory system or skin, and less frequently through the gastrointestinal tract, causing an immediate inflammatory response. Mucormycosis is classified clinically according to anatomic location, such as Rhino-orbital-cerebral (ROCM), pulmonary gastrointestinal, cutaneous, and renal mucormycosis. Patients with diabetes mellitus, hematological malignancy and chemotherapy, hematopoietic stem cells, and solid-organ transplant recipients on immunosuppressive therapy, with iron overload, on peritoneal dialysis, extensive skin injury, HIV infection, and voriconazole therapy are at a higher risk of developing mucormycosis. Diabetes mellitus is the most prevalent risk factor in Asia, whereas, in Europe and the United States, hematological malignancies and transplantation are the most common risk factors. Individuals with diabetes mellitus are more likely to develop rhino-cerebral mucormycosis, whereas patients with hematological malignancy and transplant recipients are more likely to develop pulmonary mucormycosis.[1,2]

Background
Friedrich Küchenmeister may have described the first instance of mucormycosis in 1855. In 1876, Fürbringer was the first to describe the pulmonary illness. In 1884, Lichtheim discovered how the illness spreads in rabbits and named two species: Mucor corymbifera and Mucor rhizopodiformis, which was known as Lichtheimia and Rhizopus, respectively. It was linked to poorly managed diabetes in three patients in 1943, with significant sinus, brain, and eye involvement. Saksenaea vasiformis, which was shown to cause numerous cases, was identified from Indian forest soil in 1953, and P. C. Misra looked at soil from an Indian mango grove and identified Apophysomyces, which was later discovered to be a significant cause of mucormycosis. Since then, other Mucorales species have been discovered. When instances were first recorded in the US in 1955, the author assumed it was a novel illness caused by antibiotics, ACTH, and steroids. Potassium iodide was the sole therapy accessible until the second part of the twentieth century. Survival was shown to be better in those who got combination surgery and medicinal therapy, primarily with amphotericin B, in a study of cases affecting the lungs identified via flexible bronchoscopy between 1970 and 2000.
Sign & Symptoms

A sinus infection (sinusitis) is the most frequent symptom, which is accompanied by nasal congestion, nasal discharge, and sinus discomfort. Mucormycosis can also extend to the brain. This might result in lethargy, seizures, slurred speech, partial paralysis, cranial neuropathies, a brain abscess, altered consciousness. This illness is known as rhinocerebral mucormycosis when it affects the sinuses and brain. When the infection spreads to the eye, it can cause swelling (periorbital edema), bulging or displacement of the eye (proptosis), vision loss, and perhaps blindness. When spores are breathed in and reach the respiratory system, mucormycosis can damage the lungs (pulmonary mucormycosis). Pulmonary mucormycosis is a fast progressing infection marked by fever and a cough that produces no mucus (nonproductive cough). Spitting or coughing up blood (hemoptysis), chest discomfort, and trouble breathing (dyspnea) are less common symptoms. When mucormycosis affects the skin (cutaneous mucormycosis), afflicted persons may develop a single, painful, hardened patch of the skin and inflammation of the underlying tissue. The skin around the affected area may become reddish, heated, puffy, and painful. Open sores (ulcers) and blisters can develop, and tissue loss (necrosis) can ensue, resulting in the afflicted tissue appearing black. The gastrointestinal system can also be impacted. This is most likely to happen when spores are inhaled and ingested, or when infected food is consumed. Abdominal discomfort and blood vomiting (hematemesis) are common symptoms (NORD; National Organization for rare disorders).

Epidemiology

Mucormycosis occurs in approximately 1.7 cases per 10,00000 people per year, or 500 patients per year in the United States. Mucormycosis is becoming more common around the world, but it is especially prevalent among diabetic patients in India and China. However, a recent review of 851 cases from January 2000 to January 2017 found that the disease burden is higher in Europe than in Asia, with 34 percent in Europe, 31 percent in Asia, 28 percent in North or South America, 3 percent in Africa, Australia, and New Zealand, and 3 percent in Africa, Australia, and New Zealand. The discrepancy might be attributable to Asian nations’ under-reporting during this period. In truth, India is reporting an increasing number of instances. The global burden of severe fungal diseases has been assessed by the Leading International Fungal Education (LIFE) site. Except for India, they estimate that the yearly prevalence of mucormycosis is about 10,000 cases worldwide. The worldwide estimate of mucormycosis increased to 910,000 cases with the addition of Indian data. The estimated
mucormycosis burden in various nations. Europe (from 0.2 occurrences in Denmark to 95 cases in Portugal), the United States (3.0 cases), and Australia were the continents with the highest estimated incidences per million populations (0.6 cases). A computational approach estimated the prevalence of mucormycosis in India to be 140 cases per million people, with the prevalence ranging from 137,807 to 208,177 cases per million people, with a mean of 171,504 (SD: 12,365.6; 95 percent CI: 195,777–147,688) cases per year and mean attributable mortality of 65,500 (38.2 percent) per year.^[3]  

**Pathogenesis**

Inhalation of fungal spores is the predominant route of infection in the sinus. Most Mucorales produce spores that are small enough (3–11 mm) to reach the distal alveolar spaces. Sinusitis can be caused by larger spores (>10 mm) lodged in the nasal turbinates. Even in immunocompetent hosts, inhalation of a high spore inoculum, such as during construction in polluted air ducts, can cause subacute sino-PMs. As a result, mucormycosis is uncommon in individuals with a good innate immune response, but it can be deadly in neutropenic patients. Patients on high-dose steroids are another high-risk category for mucormycosis because glucocorticoids impede macrophage migration, ingestion, and phagolysosome fusion.^[4,5]  

---

**Fig. 1: Pathogenesis of mucormycosis.**
Rhinocerebral mucormycosis

Mucormycosis rhinocerebral (sinus and brain) is a sinus infection that can migrate to the brain. People with uncontrolled diabetes and those who have had a kidney transplant are more likely to develop this kind of mucormycosis.

Saprophytic fungi cause rhinocerebral mucormycosis, a rare opportunistic infection of the sinuses, nasal passages, oral cavity, and brain. The illness has the potential to kill you quickly. Rhinocerebral mucormycosis also affect people who are immunocompromised. Mucormycosis comes in a variety of types, including lingual, pulmonary, cutaneous, gastrointestinal (GI), and disseminated.

Pathophysiology of rhinocerebral mucormycosis

The infection begins in the nasal cavity and spreads to the paranasal sinuses next to it. It is implanted in the nasal cavity and grows in the sinuses. Fungi thrive in the humid environment of the nose and paranasal sinuses, which encourages their development and invasion. The length, host immunity, and severity of the illness all play a role in the invasion of mucosa and bone. Early fungus implantation in the maxillary sinus is frequent, with a mass of fungal growth known as a fungal ball and little bone degradation. The middle turbinate is the most commonly implicated location in mucor, followed by the middle meatus and septum. In Rhinocerebral Mucormycosis, the sphenopalatine and internal maxillary arteries are involved in the invasion of the brain and orbit. Only in the most severe cases of the internal carotid artery and cavernous sinus thrombosis is the internal carotid artery and cavernous sinus thrombosis involved. In diabetic patients, especially those with diabetic ketoacidosis, infection is more common. Hyperglycemia lowers the body's immunity. Patients with
diabetes have lower leukocyte phagocytosis, neutrophil chemotaxis, and local inflammatory responses. Rhizopus thrives in a ketone-reductase system, glucose-rich media, and low oxygen tension, all of which are typical of diabetes. Bacteria and fungus both require iron to thrive. The application of an iron chelator (deferoxamine) enhances fungal virulence by making iron accessible in a suitable form for fungal development. Unsaturated serum transferrin suppresses fungal growth and functions as a fungistatic agent. Iron chelators alter transferrin's fungistatic action while simultaneously inhibiting the formation of free radicals by iron-catalyzed peroxidase, which kills fungi. Deferoxamine also masks amphotericin B antifungal action.\[6\]

**Pathophysiology of mucormycosis**

![Pathophysiology of mucormycosis](image)

**Fig. 2: Pathophysiology of mucormycosis.**
Clinical features
Despite recent advancements in diagnosis and treatment, Mucormycosis is a life-threatening infection with a high death rate. The goal was to describe 14 cases of mucormycosis infection and conduct a literature review. In a tertiary-care teaching hospital in northern Mexico, we studied the demographic and clinical data of 14 consecutive patients who presented with MCM. The patients were 39.9 years old on average (range 5–65). Males made up nine of the patients. The underlying illness in ten individuals was diabetes mellitus, while six patients had a hematological malignancy (acute leukemia). Three of the diabetic patients had chronic renal failure, while the other four had diabetic ketoacidosis. Rhinocerebral involvement was present in all of the patients. The mortality rate at the hospital was 50%. All of the patients were treated medically with polyene antifungals, and 11 of them were also treated surgically.\[7\]

Clinical diagnosis
Mucormycosis should be extensively investigated in a patient with diabetes and sinusitis. In individuals with diabetes mellitus, a strategy for the diagnosis and management of rhinocerebral mucormycosis was developed. In this method, cranial nerve palsy, diplopia, sinus discomfort, proptosis, periorbital edema, orbital apex syndrome, or a palatine ulcer are the "red flags/warning signals." Neutropenia is the most common cause of pulmonary mucormycosis. Clinically, it's difficult to tell the difference between pulmonary aspergillosis and fusariosis. The reverse halo sign (RHS) on a computed tomography (CT) scan is another indication of mucormycosis. Sequential thoracic CT scans were conducted in leukemic neutropenic patients in the research of Legouge et al., and the RHS was seen in 15 of 16 patients (94 percent) during the first week of the illness, whereas other radiologic abnormalities, such as numerous nodules, occurred later. These observations led the investigators to the conclusion that the presence of the RHS on CT was a significant indication of pulmonary mucormycosis in neutropenic leukemic individuals with lung infection.\[8,9\]

Histopathology
The presence of fungal hyphae typical of mucormycetes in biopsies of afflicted tissues or bronchoalveolar lavage (BAL) in individuals with pulmonary mucormycosis leads to a definite diagnosis. Histopathology is a critical diagnostic technique because it separates the
presence of fungus as a pathogen in the material from a culture contaminant and is required to determine whether blood vessel invasion has occurred.[10]

**Molecular assays**

Traditional polymerase chain reaction (PCR), restriction fragment length polymorphism analyses (RFLP), DNA sequencing of specified gene areas, and melt curve analysis of PCR products are all examples of molecular-based tests. All of the above tests can be used to detect or identify Mucorales. Molecular-based diagnostic assays are now suggested as important add-on tools to augment traditional diagnostic methods.[11,14]

**Treatment**

Most antifungals, including voriconazole, are resistant against Mucorales fungus in vitro. Except for some *Cunninghamella* and *Apophysomyces* isolates, Amphotericin B is the most active medication. Posaconazole and isavuconazole are also active, while itraconazole and terbinafine have modest efficacy against select strains. The European Conference on Infections in Leukemia (ECIL-6) recommendations from 2016 as well as the ESCMID/ECMM guidelines recommend using a lipid formulation of amphotericin B as first-line therapy for mucormycosis. Isavuconazole is a newly discovered triazole having antifungal action against Mucorales and other fungal species. Finally, the experimental medication VT-1161, a fungus-specific inhibitor of CYP51, has shown in vitro efficacy against Mucorales, including *R. oryzae*. VT-1161 was found to prolong the lifespan of neutropenic mice with mucormycosis caused by *R. oryzae*, *Lichtheimia*, and *Cunninghamella*. *oryzae*, when used therapeutically or as a preventative measure. Although more research is needed to determine the efficiency of VT-1161 against other Mucorales (higher MIC values were seen against *R. Delmar*), this ergosterol synthesis inhibitor might be a useful addition to our mucormycosis arsenal.[15-21]

**CONCLUSION**

To summarize, Mucormycosis is a life-threatening infection that most often affects immunocompromised patients and that, despite vigorous multimodal therapy, has a high death rate. Diabetes mellitus is the most common underlying illness worldwide, according to new findings. The diagnosis of mucormycosis is still difficult. Although molecular techniques are advancing, histopathology, direct inspection, and culture remain important tools. The rhino-orbital-cerebral cavities were the most often affected in our patients, and DM was the most prevalent underlying illness. Unfortunately, in third-world countries, the use of
liposomal amphotericin B is typically prohibitive due to financial constraints, therefore our patients were instead treated with conventional amphotericin B.

REFERENCES


3. Hariprasath Prakash, Arunaloke Chakrabarti et.al Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh. Global Epidemiology of Mucormycosis, 2019.

4. Dimitrios Farmakiotis, Dimitrios P. Kontoyiannis, et.al Division of Infectious Diseases, Rhode Island Hospital, Warren Alpert Medical School of Brown University, 593 Eddy Street, Providence, RI 02903, USA. Mucormycosis, 2016.

5. Arunaloke Chakrabarti, Rachna Singh et. al Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. Unique features of Mucormycosis in India, 2014.

6. Jenish Bhandari.et.al, Antifungal effect of amphotericin B.


