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Review Article

# Mucormycosis

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## Abstract

Mucormycosis is a rare fungal infection that is seen predominantly in immunosuppressed individuals. There has been an upsurge of cases during the COVID-19 pandemic. Iron plays a vital role in the pathogenesis. The disease may manifest in various types. Globally, the most common form is rhino orbito cerebral mucormycosis (ROCM). The fungi can cause angioinvasion and tissue necrosis. Early diagnosis, surgical debridement and prompt initiation of appropriate anti-fungal therapy plays an important part in determining the course of illness. The mortality rate ranges from 28 - 52%.

**Keywords:** Mucormycosis; Immunosuppression; COVID-19; Iron; Angioinvasion; Mortality

## Abbreviations

AmpB: Amphotericin B; CNS: Central Nervous System; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease 19; CT: Computed Tomography; DKA: Diabetic Ketoacidosis; DM: Diabetes Mellitus; GI: Gastrointestinal; GMS: Gomori Methanamine Silver; GVHD: Graft Versus Host Disease; H&E: Haematoxylin and Eosin; HM: Haematological Malignancy; HSP: Heat Shock Proteins; IFN-γ: Interferon Gamma; IVDU: Intravenous Drug Use; MRI: Magnetic Resonance Imaging; NK Cell: Natural Killer Cell; PAS: Periodic Acid Schiff; RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted; ROCM: Rhino-Orbito-Cerebral Mucormycosis; SOT: Solid Organ Transplantation

## Introduction

Mucormycosis also known as "black fungus" is an invasive infection caused by filamentous fungi of Mucorales order and class Zygomycetes [1,2]. They are also called zygomycosis or phycomycosis [3]. 11 genera and around 27 species can cause human infections [4]. The common organisms causing this infection belong to genus *Rhizopus, Lichtheimia* and Mucor [4]. Globally, the most common agent isolated is *Rhizopus arrhizus* followed by *Apophysomyces* species in India and Lichtheimia species in developed countries [5]. Though rarely, species of *Rhizomucor, Cunninghamella* and *Saksenaea* are also implicated in this disease. It was first described by Paultauf in 1885 [6]. They invade into the blood vessels and are associated with high morbidity and mortality rates [1,7,8]. It mainly affects the immunosuppressed individuals and the prevalence is rising nowadays amidst rising COVID-19 cases [5]. This review highlights the pathophysiology, predisposing factors, clinical features, diagnostic modalities, current management and preventive strategies based on the current understanding.

## Epidemiology

There is a global rise in incidence of cases over the past decade. Based on the recent review done from 2000 to 2017 by Jeong., et al. of 851 cases, Europe (34%) had more cases than Asia (31%) followed by North or South America (28%), Africa (3%), Australia (3%) and New Zealand (3%) [9]. Population based survey conducted in India showed an increase in cases from 24.7 cases per year in 1990 - 2007 to 89 cases per year in 2013 - 2015 [10]. This is inspite of the marked under reporting of cases due to a decline in autopsy. The annual prevalence is 910000 globally [4]. In India, the incidence is 0.14 per 1000 inhabitants which is 80 times more than that seen in developed countries [11]. The numbers are rising more so now, as it is seen along with or after COVID-19 infection. It may be because of the infection itself or because of the milieu created by immunosuppressants including steroids.

Most infections occur via inhalation of fungal spores in the air while it can also occur through direct inoculation into wounds or by ingestion of contaminated food [12-14].

## Predisposing factors

It is seen commonly in immunosuppressed individuals including patients with Diabetes Mellitus, Diabetic ketoacidosis (DKA), haematological malignancy (HM) with or without stem cell transplantation, prolonged and severe neutropenia, long term use of immunosuppressants, solid organ malignancies and solid organ transplantation (SOT), hemodialysis, chronic kidney disease, major trauma, post tuberculosis, iron overload and chelation therapy with desferrioxamine, illegal intravenous drug abuse, neonatal prematurity and malnourishment [15].

While Diabetes Mellitus is the most common underlying factor in Asia, it is haematological malignancies and transplantation in Europe and USA [10,13,16].

In India, Diabetes Mellitus was the predominant risk factor identified in over 50% of cases as compared to Europe where haematological malignancy and transplantation was implicated in 38 - 62% of cases according to various studies [4].

Even though, increased incidence of mucormycosis is seen with Deferoxamine, they have not been seen with other chelators like Deferasirox [17,18].

Immunocompetent patients may develop cutaneous mucormycosis after trauma, burns, surgery and contaminated dressings. In India, cutaneous type and isolated renal mucormycosis are common in immunocompetent patients [19]. Healthcare associated mucormycosis has been described after use of contaminated tongue depressors, wound dressings and umbilical catheters. It was predominantly cutaneous followed by GI, pulmonary, sinuses and brain [4].

In a study conducted across India by Patel., et al. out of 465 cases, the risk factors for the development mucormycosis were identified as DM, SOT, HSCT, HM and solid organ malignancy, trauma, pulmonary disease (Tuberculosis, COPD, asthma), neutropenia, steroid therapy, chronic kidney disease, HIV and miscellaneous in 73%, 6.5%, 1.3%, 9%, 7.5%, 6.5%, 2.6%, 3.7%, 20%, 1.5% and 30.8% respectively [20]. 11.8% were immunocompetent. Miscellaneous included septicemia, hematological disorders (aplastic anaemia, pancytopenia), autoimmune disease, liver disease, prematurity, bowel perforation, GVHD, IVDU, iron chelation therapy, high risk neonates, immunosuppressant drugs, cardiovascular and neurological disease.

## COVID-19 and mucormycosis

Globally, the cases of mucormycosis has increased in the COVID-19 era [21]. The number of COVID-19 patients globally and in India reported are 173,005,553 and 28,909,975 respectively as of June 7, 2021. Over 12,000 cases of mucormycosis have been reported in India within this period associated with COVID-19 (during or post COVID-19). COVID-19 by itself, is known to cause lymphopenia and thereby a decline in cell mediated immunity which is known to be a predisposing factor for invasive fungal infections [22,23].

Apart from the risk factors we have mentioned above, whether the increased use of steroids and monoclonal antibodies for the treatment of COVID-19 has a role or is it due to the immune alterations occurring as a part of COVID-19 has to be studied [24].
(Table 1)

## Pathogenesis

Mucormycosis is caused by fungi, a free living organism seen abundantly in soil. It is mostly seen as contaminants in biological specimen and is not of much significance unless obtained from sterile sites (Figure 1).

| | |
|---|---|
| Diabetes Mellitus | Haemodialysis |
| Diabetic ketoacidosis (DKA) | Chronic kidney disease |
| Haematological malignancy (HM) with or without stem cell transplantation | Major trauma |
| Prolonged and severe neutropenia | Post tuberculosis |
| Long term use of immunosuppressants | Iron overload and chelation therapy with desferrioxamine |
| Solid organ malignancies and solid organ transplantation (SOT) | Intravenous drug abuse |
| | Neonatal prematurity and malnourishment. |

**Table 1:** Risk factors for mucormycosis.

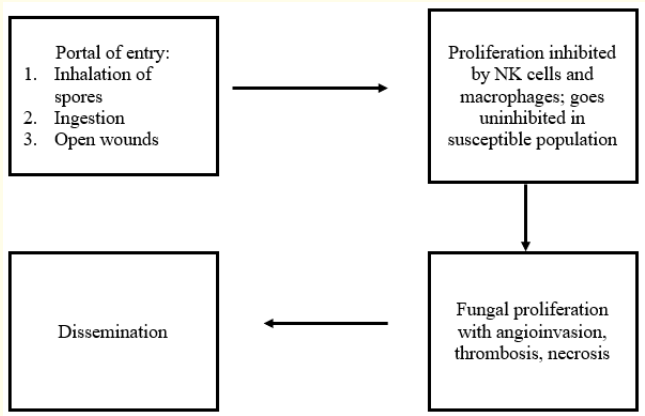


**Figure 1:** Pathogenesis.

Iron uptake from the host plays a central role in the pathogenesis [25-27]. This happens mainly by the following means. Firstly, the fungi have iron permeases through which they can acquire iron from the host. Secondly, *Rhizopus* also secrete rhizoferrin which is a siderophore and helps acquire iron through receptor mediated energy dependent process. Finally, they can also obtain iron from heme with the help of heme oxygenases.

They invade the blood vessels and result in thrombosis and tissue necrosis [28]. It helps in dissemination of the fungus. This is with the help of a glucose regulated protein (GRP78), belonging to the family of HSP70 that aid in penetration and endothelial damage [29,30].

In patients with uncontrolled Diabetes and DKA which causes hyperglycaemia and low pH, the phagocytes become dysfunctional and lead to impaired chemotaxis and defective intracellular killing [31]. The increased glucose and acidotic environment up regulates the fungal receptors in the cell surface thereby facilitating their entry into the cell and also up regulates GRP78 which aids in their multiplication and dissemination [29]. The fungal hyphae of *Rhizopus* also cause an immunosuppression by reducing secretion of the NK cells such as IFN-γ, RANTES [32]. Diminished cell mediated immunity also favour the development of invasive fungal infections.

## Modes of transmission

1. Inhalation of fungal sporangiospores may result in rhino cerebral and pulmonary mucormycosis [1]. They can then penetrate the cribriform fossa and reach brain.
2. Direct inoculation into open wounds, contaminated instruments can result in cutaneous type [14].
3. Ingestion of contaminated food may result in GI mucormycosis [14].
4. They are angioinvasive and spread directly through the blood stream and may get disseminated to various parts of the body.

## Types and clinical features

The main feature of this disease is angioinvasion, vessel thrombosis and tissue necrosis.

6 types of mucormycosis are seen (Table 2). The most common is rhino-orbito-cerebral mucormycosis (ROCM). Others include cutaneous, pulmonary, gastrointestinal, disseminated and uncommon varieties [1]. Globally, the most common sites include sinuses (39%), lungs (24%) and skin (19%). As per the Indian data, ROCM (45 - 74%) is the commonest form followed by cutaneous (10 - 31%), pulmonary (3 - 22%), renal (0.5 - 9%), GI (2 - 8%) and disseminated forms (0.5 - 9%) [5].

In the rhino orbito cerebral type, mainly the nose, sinus cavities and brain are affected. They invade the sinuses and can result in sinusitis, epistaxis, headache. They can also cause peri orbital cellulitis, external ophthalmoplegia and vision loss. A black necrotic eschar is characteristic [15].

| Site of infection | Percentage of cases |
|---|---|
| ROCM | 25 - 39% |
| Pulmonary | 24 - 30% |
| Cutaneous | 19 - 26% |
| Gastrointestinal | 2 - 11% |
| Disseminated | 15 - 23% |
| Uncommon (bones, joints, heart, peritoneum) | Rare |

**Table 2:** Clinical types of mucormycosis [14].

Pulmonary type may present as cough, hemoptysis, dyspnoea and may be misdiagnosed as Aspergillosis. Radiological findings like cavity, consolidation, nodules, atelectasis, effusion and mediastinal lymphadenopathy may be seen. Voriconazole used in the treatment of aspergillosis is not effective against mucormycosis.

Cutaneous type is seen in patients with road traffic accidents and contaminated implants through which the organism is directly inoculated. They may be seen as black necrotic eschar, plaques resembling Tinea corporis and as gangrene.

GI mucormycosis is usually acquired by ingestion of contaminated milk, bread, alcoholic beverages or herbal products. Stomach is the most commonly affected part followed by colon and ileum [33]. They may present either as mass or perforation with upper GI bleed. They may present in premature neonates as necrotising enterocolitis. They can also affect liver, spleen and pancreas. Upper GI bleed, bowel perforation, peritonitis and sepsis are the common causes of death.

In the disseminated type, brain (90%) is the most common organ affected [1,34,35]. Pulmonary variant has the highest incidence of dissemination [36]. It has a mortality of more than 90% [37].

Uncommon forms may present as endocarditis especially of prosthetic valve, osteomyelitis, peritonitis or pyelonephritis [38-41]. Case reports of mucormycosis causing SVC syndrome, affecting mediastinum and trachea, breast, ear and spine have been published [42-46].

## Diagnosis

Early diagnosis warrants high clinical suspicion. Imaging in the form of CT/MRI of the appropriate part helps in assessing the extent of disease along with vascular status.

The condition is mainly diagnosed via biopsy. The specimen can be obtained through surgical or endoscopic means. Direct microscopy with tissue staining using H&E, PAS or GMS staining reveal hyphae which appear as broad, ribbon like with irregular branching, aseptate hyphae situated at right angles to each other (Figure 2) [15,47]. Infected areas also show signs of necrosis and they also invade the blood vessels causing thrombosis.

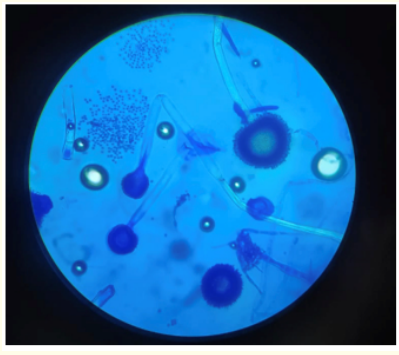

**Figure 2:** Nonseptate broad hyphae of mucor with sporangiospores.

Acute lesions may be seen as haemorrhagic infarction, coagulative necrosis, angioinvasion, neutrophilic infiltration and perineurial invasion. Splendor Hoeppli phenomenon, which is deeply eosinophilic material surrounding the pathogen may be seen in chronic cases [48]. Granulomatous inflammation and giant cells may also be seen.

IHC with monoclonal antibodies have been shown to be very sensitive and specific but they are not routinely available. PCR techniques are also helpful in diagnosis.

Culture of the tissue helps in identification of species and genus along with assessment of anti fungal susceptibility.

## Treatment

The most important factors affecting the prognosis are early diagnosis, correcting the underlying factors, surgical debridement of infected tissue and anti fungal therapy [14].

The antifungals used are Amphotericin B deoxycholate (AmpB), liposomal Amphotericin B, Ivasuconazole and Posaconazole [14].

Amphotericin B: It was one of the oldest antifungals discovered which had very high efficacy against mucormycosis. It is usually used in the dosage of 0.2 - 0.5 mg/kg/day in Dextrose infusion. The side effects include hypoglycaemia, electrolyte imbalances, nephrotoxicity and cardiac arrhythmias. The safer alternative discovered was liposomal amphotericin B which can be used when there is no CNS involvement. It had significantly improved side effect profile. The dosage recommended is 5 - 10 mg/kg/day [15]. The duration of treatment may range from weeks to months. Treatment to be continued till there is clinical improvement and complete resolution on imaging.

The newer antifungals, isavuconazole and posaconazole have also showed good efficacy against mucormycosis with the former better than latter [49].

Occasionally these antifungals are combined with each other or with Echinocandins but it has not significantly increased their effectiveness.

Surgical debridement of the part if necessary should be done as they interfere with the blood supply of the affected part and their removal helps in improving the penetration of the antifungals [50].

Role of hyperbaric oxygen therapy and cytokine therapy are still unclear [51,52].

### Prognosis

Localised sinonasal disease has good prognosis with less than 10% mortality after successful debridement [36]. Pulmonary and disseminated variants have poor prognosis with mortality rate ranging from 60-100%. Overall mortality rates vary from 40 - 80% as per various studies depending on the species, location of involvement and underlying nature of illness [10,53]. The mortality rate in India ranges from 28 to 52%. The mortality rate in various clinical forms as per Indian data are: ROCM (31 - 49%), pulmonary (61 - 77%), cutaneous (23 - 57%), GI (67 - 94%) and disseminated (62-79%) [5].

### Prevention

As the idiom says “prevention is always better than cure". The predisposed individuals should be strictly followed up in order to pick early signs of infection. In case of infection, immunosuppressants should be stopped, appropriate control of Diabetes and its complications including DKA should be ensured. In case of malignancy, chemotherapy may have to be stopped or if the aggressive nature of malignancy is the cause, it has to be appropriately controlled. In this COVID-19 era, judicious use of steroids along with use of face masks and ensuring personal hygiene play an important role in preventing this disease.

## Conclusion

Mucormycosis is an aggressive fungal infection usually seen in immunosuppressed individuals with high mortality rate and there has been a recent surge in cases along with the COVID-19 pandemic. The role of iron metabolism in the pathogenesis is highlighted. The various types and presentation has been described. Early diagnosis, nature of underlying illness, surgical debridement along with appropriate anti fungal therapy plays a crucial role in management of this disease. The various steps that need to be taken to prevent the infection has also been highlighted.

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