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REVIEW

# Risks of mucormycosis in the current Covid-19 pandemic: a clinical challenge in both immunocompromised and immunocompetent patients

**P. Monika**[1] · **M. N. Chandraprabha**[1]

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**Abstract**
Mucormycosis, also called "Black Fungus", is a new cause for worry in the current Coronavirus disease 2019 (covid-19) pandemic. Mucormycosis is devasting due to its high rate of morbidity and mortality which is a great cause of concern. Mucormycosis, in general, affects immunocompromised patients including diabetic, people with malignancies, organ and stem cell transplants and people affected with pandemic diseases like covid-19. Diagnosis of Mucormycosis is often delayed either due to clinical complications or misdiagnosed as symptoms of other diseases, especially covid-19. This could delay the treatment protocol which results in the failure of treatment. Mortality rate due to secondary infections in covid-19 patients with uncontrolled diabetics and who are on steroid therapy can soon reach 100% if diagnosis and treatment doesn't happen on timely basis. Risk of Mucormycosis is not just in immunosuppressed patients, but immunocompetent people with late diagnosis are also prone to infection. In view of this, we present a comprehensive review on risks of Mucormycosis in immunocompromised and immunocompetent patients highlighting the epidemiology, forms of Mucormycosis, immune response against Mucorales, difficulties in diagnosis and challenges in treatment of Mucormycosis, with emphasis on covid-19 associated Mucormycosis. Importantly, we have discussed the precautions and care to effectively manage Mucormycosis in immunocompromised and immunocompetent patients. Thus, current review helps clinicians in understanding various risk factors in both immunocompromised (especially covid-19 patients) and immunocompetent patients which is critical in managing Mucormycosis in current covid-19 pandemic.

**Keywords** Black fungus · Covid-19 · Immunocompetent · Immunocompromised · Mucormycosis · Risks of mucormycosis

## Introduction

Mucormycosis, also known as Zygomycosis, can be defined as an insidious fungal infection caused by members of Mucorales and zygomycotic species. The term "Mucormycosis" was coined by American pathologist R.D. Baker [1]. The first case of Mucormycosis was reported by German pathologist Paltauf in the year 1885 [2]. Humans acquire the infection predominantly by inhalation of sporangiospores, occasionally by ingestion of contaminated food or traumatic inoculation [3]. Eleven genera and − 27 species under Mucorales are associated with human infections, but the most common causative agent of Mucormycosis that is reported globally is *Rhizopus arrhizus*, followed by *Lichtheimia, Apophysomyces, Rhizomucor, Mucor and Cunninghamella species* [4]. Nevertheless, there are diverse of species that cause fungal infection in various forms of Mucormycosis as seen in the clinical isolates. This could be a major concern and remains a challenge for clinicians to treat the disease.

## Forms of Mucormycosis

Mucormycosis rarely occurs in a healthy individual but increasingly recognized in immunocompromised patients. It can be categorized into rhino-orbito-cerebral, cutaneous, disseminated, gastrointestinal, and pulmonary types. Data collected from Prakash and Chakrabarti suggested that, in

✉ M. N. Chandraprabha
chandra@msrit.edu

[1] Department of Biotechnology, M.S. Ramaiah Institute of Technology, MSR Nagar, MSRIT Post, Bangalore, Karnataka 560054, India

India of all the above types, rhino-orbito-cerebral is the most common form of the disease followed by the pulmonary and cutaneous types, with cutaneous type most commonly seen in patients with trauma or burns. They also suggested that isolated renal Mucormycosis in a healthy host is a unique clinical presentation in India which according to us is quite interesting yet alarming [5]. Representative characteristics of different forms of Mucormycosis such as most commonly infected organ, prevalence in different people and symptoms are discussed in Table 1. Reported case studies and survival vs. mortality rate of different clinical forms of Mucormycosis is shown in Fig. 1A, B respectively.

## Global epidemiology

The survival rate for rhino-orbito-cerebral disease in patients without any systemic disease is about 75%; with other diseases is about 20%; and in pulmonary disease is considered to be fatal. Data collected by Suganya et al. (2019) described the survival rate in different forms of Mucormycosis that varies with foci of the infection: rhino-orbito-cerebral Mucormycosis – 45%, focal cerebral Mucormycosis – 33%, pulmonary Mucormycosis – 36%, sinusitis without cerebral involvement – 87%, cutaneous isolated – 90%, disseminated disease – 16%, and involvement of gastro intestinal form – 10% [6]. Unfortunately, the mortality rate is high which makes Mucormycosis a devastating disease. In a recent study conducted in India by Prakash and Chakrabarti (2021) in gastro intestinal form showed highest mortality rate of 66.7%, followed by disseminated (61.5%), pulmonary (61.3%), cutaneous (57.1%), renal (50%) and rhino-orbito-cerebral (48.6%) [5]. The mortality can soon reach 100% if not diagnosed and treated timely. Though Mucormycosis is globally distributed, certain risk factors and clinical forms contribute to its estimated prevalence to around 70 times higher in India than that in global data [5]. In the world, India is the most affected country with 44.3% immunocompetent patients infected with Mucormycosis, followed by USA (19.8%) and Australia (5.7%). Most common representative clinical form is the cutaneous/subcutaneous type with 42.5% patients [7]. Global epidemiology of prevalence of Mucormycosis is shown in Fig. 1C.

## Immune response against Mucorales

Immune system and its competence to fight against the fungi play an important role in controlling the spread of clinical manifestations of the disease and thus reduce mortality. Entry of spores into the body happens via 2 main routes: respiratory route or cutaneous. Mucorales attack deep tissues by means of ingestion or inhalation of spores, and percutaneous

**Table 1** Representative characteristics of different forms of Mucormycosis

| Form of Mucormycosis | Part of the body mostly affected | Type of population commonly seen in | Symptoms | References |
|---|---|---|---|---|
| Rhino-orbito-cerebral | Brain | Uncontrolled diabetes, kidney transplant patients | Fever, one-sided facial swelling, headache, nasal or sinus congestion, black lesions on nasal bridge or upper inside of mouth that quickly become more severe | [78, 79] |
| Pulmonary Mucormycosis | Lungs | Cancer, organ transplant or stem cell transplant patients | Fever, cough, chest pain, shortness of breath | [25, 80] |
| Gastrointestinal Mucormycosis | Stomach, colon and intestine | Young children, especially premature infants less than 1 month of age, who have had medications, surgery | Abdominal pain, nausea and vomiting, gastrointestinal bleeding | [81, 80] |
| Cutaneous Mucormycosis | Damaged skin such as cuts, burns, wounds or other type of skin trauma | both immunocompetent and immunocompromised individuals with higher prevalence in immunocompetent individuals | Darkened skin, blisters or ulcers, pain, warmth, excessive redness, or swelling around a wound | [82][79] |
| Disseminated Mucormycosis | Brain, spleen, heart, and skin | Immunocompromised patients | Fever, chills, green, mucopurulent sputum | [79, 83] |

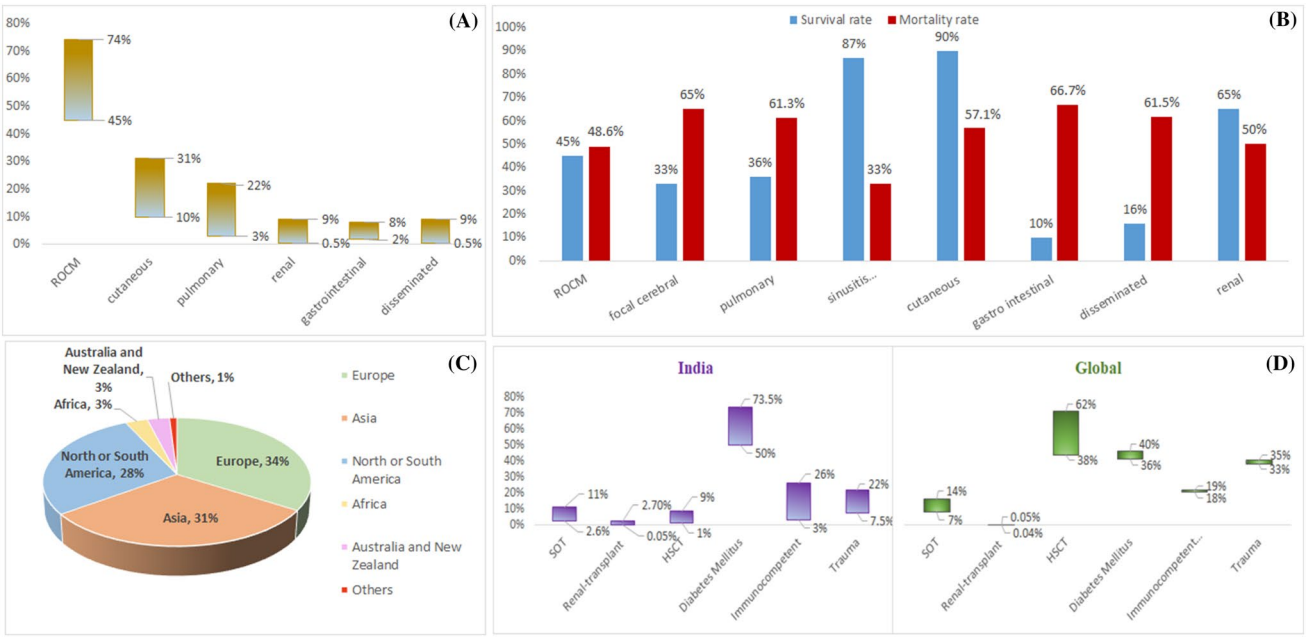


**Fig. 1** Reported case studies of different forms of Mucormycosis (**A**). Survival and Mortality rate in different forms of Mucormycosis (**B**). Global epidemiology of prevalence of Mucormycosis (**C**). Major risk factors that cause Mucormycosis in India and globally (**D**). *ROCM* Rhino-orbito-cerebral Mucormycosis; *HSCT* Hematopoietic stem cell transplantation; *SOT* solid organ transplantation

injection of spores by tainted needles. Once they enter into the deep tissues of a healthy individual, they need to fight with the first line of immune defence. In a healthy host, immune system is capable of destroying the spores via oxidative metabolites and cationic peptides [8]. We describe the roles and functions of different immune cells and the kind of immune response against Mucorales in a healthy individual.

Neutrophils are key players in fighting against Mucorales species as they are important cells in host defence system. Neutrophils are the first line of defence in the innate immune response as these cells rapidly migrate into the infected tissue, produce reactive oxygen species, and release neutrophil extracellular traps. It was observed that fungal damage was enhanced by influencing the neutrophil activity by cytokines, and is different in different microorganisms [9, 10]. However, decreased levels of neutrophils were observed in diabetes mellitus patients [11, 12]. During infection by diverse mucoralean species, leukocytes communicate with each other by producing a wide range of cytokines and chemokines. Interleukin-1 beta (IL-1β) has been described to play an important role in response to pathogenic fungi. In addition, tumor necrosis factor alpha (TNF-α), IL-6, IL-12, IL-8, Granulocyte-macrophage colony-stimulating factor (GM-CSF) helps in recruitment, survival, activation, and differentiation of neutrophils, natural killer cells, T cells, basophils, and eosinophils [13].

Macrophages are majorly involved in eradicating pathogens and iron-recycling from senescent erythrocytes [14]. Peripheral blood mononuclear cells play an essential role in both innate and adaptive immune response. Amount and type of cytokine produced by these cells may vary in response to different fungal species with production of IL-1β being highest in Mucorales [15].

T lymphocytes maintain the homeostasis of immune system, especially adaptive immune response. Among all T cells, each subset of T helper cells possesses a specific cytokine profile that modulates anti-fungal immunity by activating macrophages and neutrophils or by production of various interleukins [16]. Interestingly, importance of T cells was recognised in immunotherapy and potential use of Mucorales-specific T cells from healthy donors can be used in adoptive immunotherapy [17].

Role of Monocyte-Derived Dendritic Cells and Epithelial Cells in response to Mucorales were studied in in vitro disease models with pathogenic fungi and was found that they were involved in inflammatory cytokine and chemokine secretion [18]. Natural Killer cells are involved in production of diverse cytokines, including Interferon (IFN)-γ, TNF-α, GM-CSF, and CCL5. It was observed that Natural Killer cells exert indirect antifungal activity by modulating immune cells via the production of diverse cytokines, including IFN-γ, TNF-α, GM-CSF, and CCL5. However, an opposite kind of immune response was observed in Mucorales as the production levels of IFN-γ and the pro-inflammatory chemokine CCL5 was significantly reduced [19]. The studies on importance of B cells and their antibodies

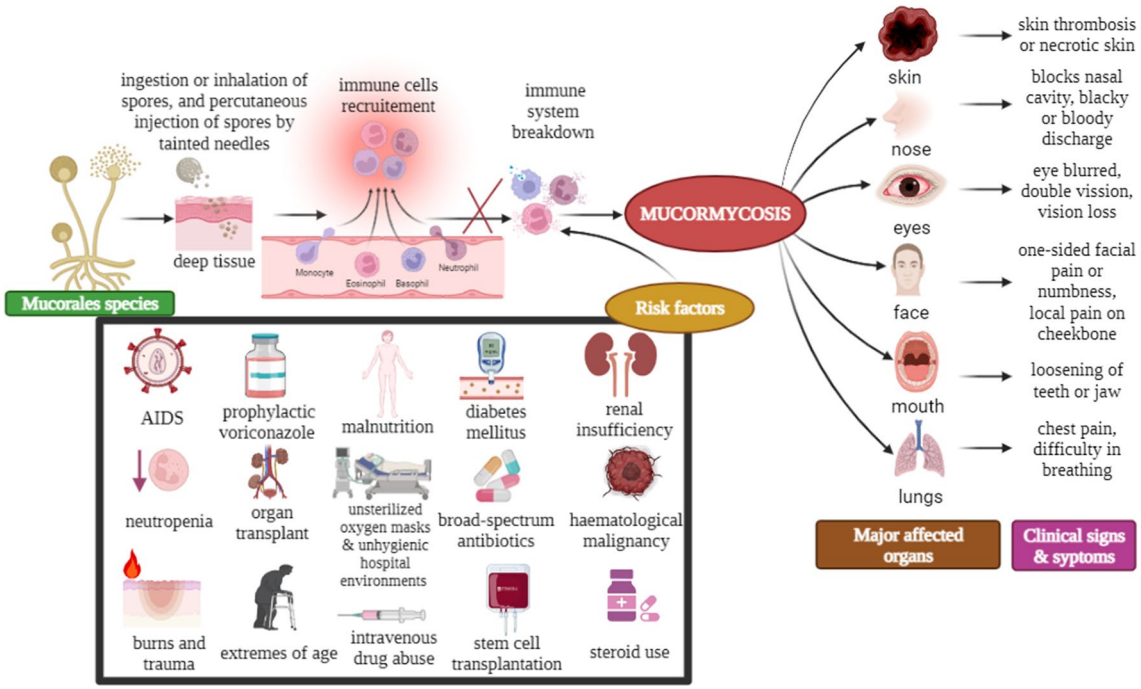


**Fig. 2** Proposed scheme for cause of Mucormycosis in both immunocompromised and immunocompetent patients. The Mucorales species (approximately 27 different types) are known to cause the infection. Initially the spores released by Mucorales enter the body deep into the tissues either by ingestion, inhalation or percutaneous injection of spores. Soon after the infection, the immune cells are recruited to fight against the foreign agents. However, due to influence of various risk factors (internal, external, local and systemic) as shown in the figure, immune sytem fails to fight against the organism and result in immune disregulation or immune system breakdown. This results in a disease called 'Mucormycosis'. Mucormycosis can affect various vital body organs including skin, nose, eyes, face, mouth and lungs. They cause various symptoms which can vary from minor amputations to major symptoms including depletion of organs and even death. This disease can be prevented or treated by timely diagnosis and effective treatment methods

against Mucorales is very scarce and we suggest it needs to be explored further. Contrastingly, in case of immunocompromised patients these immune cells are incapable of showing an optimum response due to which the production of cytokines and chemokines are significantly reduced, thus causing a higher risk of attack and severe infection in such patients.

## Risks of Mucormycosis

Risk factors of Mucormycosis include uncontrolled diabetes mellitus, especially ketoacidosis, steroid use, extremes of age, neutropenia; especially with haematological malignancy, AIDS, renal insufficiency, organ or stem cell transplantation, iron overload, skin trauma, broad-spectrum antibiotics, intravenous drug abuse, prophylactic voriconazole for aspergillosis and malnutrition [6]. However, several incidences of Mucormycosis have been reported in immunocompetent patients as well. Figure 2 represents the proposed scheme for cause of Mucormycosis in both immunocompromised and immunocompetent patients and Fig. 1D shows major risk factors that cause Mucormycosis in India and Globally. The following paragraphs highlight the clinical studies on risks of Mucormycosis in both immunocompromised and immunocompetent patients.

## Risk of Mucormycosis in immunocompromised patients

### Uncontrolled diabetes mellitus

Uncontrolled diabetes mellitus ranks top with highest risk of Mucormycosis. A recent global estimate showed that 463 million adults (20–79 years), and 1 million children and adolescents under the age of 20 live with diabetes. China and India top the diabetes chart globally with 116.4 million and 77 million cases respectively, followed by the USA (31 million) [20]. This is an alarming situation as it adds additional risks of Mucormycosis infection to the people with already pre-existing disease. In diabetic patients, Mucormycosis occurs as a destructive and potentially critical condition due to augmented availability of micronutrients and diminished defence mechanism of the body [21]. Ketone reductase present in *Rhizopus* species increases the glucose and acidic

environment. This results in ketoacidosis with increased fungal invasion in diabetes mellitus patients that aggravates the condition and risk factors that results in patient prone to all types of Mucormycosis infections [22–24]. Mucormycosis incidences in patients with diabetes as primary disease exhibited inflammatory infiltration of neutrophils, multinucleated giant cells, and phagocytes in the site of infection, as well as tissue damage and necrosis [25].

In India, diabetes is a great cause of concern for its high mortality rate. Mortality rate was reported 90% or even more with Mucormycosis, before the administration of Amphotericin B and radical surgery [26]. There were reports that indicated uncontrolled diabetes as more risk factor compared to other risks associated with patients having haematological malignancy and solid-organ transplant recipients [4]. There are various theories and research that explain the cause of attack of Mucorales in patients with uncontrolled diabetes. Ultimately, we suggest keeping the clinical conditions of diabetes at bay and early diagnosis of Mucormycosis in such patients can significantly reduce the mortality rate.

## Immunocompromised Covid-19 patients

Many people recovering from covid-19 had later been infected by Mucormycosis disease (also called as black fungus). When Mucor attacks the sinuses, it spreads to the lungs, the brain and the central nervous system. The fungus invades the sinus and makes its way into the intra-orbital and intracranial regions. 50–80% of patients are at a risk of death if not checked at early stages. If immune system is strong then the inhaled spores would be killed by immune system. On the other hand, if the immune system is weak or suppressed the spores germinate and grow rapidly as thin, wire-like tubes that branch out and enter the blood vessels and kill them. Covid-19 patients are more prone to infection as they are immunocompromised and the fungi take advantage of the same to invade the host of such patients and hence, we call such infections as opportunistic infections. This can be cured if diagnosed or treated quickly or could otherwise be fatal.

Various complications are associated with covid associated Mucormycosis, starting from mild symptoms to cardiac dysfunction leading to cardiac arrest. Sudden cardiac arrest in patients with no prior history of ischemic heart disease and Fulminant myocarditis and cardiogenic shock were observed in few cases [27]. Thus, as a precautionary measure, serial echocardiographic assessment and cardiac MRI scan is advised to post covid-19 patients after 6 weeks of presentation who had fibrosis and inflammation during the acute phase of covid [27]. Several other studies showed the possibility of Mucormycosis and Amphotericin B (causing several electrolyte imbalances) that could be the leading cause for progressive cardiac dysfunction and severe myocarditis leading to death [28, 29].

A recent systematic review reported that, 101 cases of Mucormycosis in people with covid-19 have been reported worldwide, of which 82 cases were from India among which 18 (out of total 31) expired due to several complications [30]. India is the second leading country with most diabetic burden with highest death due to the disease, which may be one of the major factors for increasing the number of deaths in patients with covid associated Mucormycosis [31]. Apart from India, Asian countries like, Iran, Pakistan, Nepal and Bangladesh have also reported covid associated Mucormycosis cases [32]. A recent study conducted by Ahmadikia et al. (2021) concluded that severe viral pneumonia, accentuated by other risk factors, makes patients prone to Mucormycosis. In particular rhino-orbital-cerebral, pulmonary, gastrointestinal and disseminated Mucormycosis were seen in covid-19 associated Mucormycosis with rhino-orbital-cerebral being the most predominant type [33]. Pulmonary Mucormycosis being the second prominent type, requires a high degree of clinical suspicion to diagnose in covid-19 patients. Another study conducted by Sharma et al. (2021) studied the possible association between invasive fungal sinusitis (Mucormycosis) and coronavirus disease in 23 patients. They observed that all the 23 subjects diagnosed with Mucormycosis had association with covid-19 and all had a history of steroid use during their coronavirus treatment, 21 out of 23 had diabetes and 12 had uncontrolled diabetes [34]. Few other studies conducted recently also described the association of high risks of Mucormycosis in covid-19 patients [35, 36]. Currently, use of steroids for covid-19 patients pose huge risk for Mucormycosis infection.

Steroids are life-saving treatment for severe and critically ill covid-19 patients. Several treatment options have been evaluated, none except systemic glucocorticoids have been shown to improve survival in covid-19. Glucocorticoids are one of the drugs proven to be beneficial in covid-19 as they reduce mortality in hypoxemic patients with covid-19. Nevertheless, glucocorticoids can increase the risk of secondary infections. Moreover, the immune dysregulation caused by the virus and the use of concurrent immunomodulatory drugs such as tocilizumab, dexamethasone could further increase the risk of infections in covid-19 patients [33, 37, 38, 33].

Doctors believe Mucormycosis, which has an overall mortality rate of 50–80%, may be triggered by the use of steroids. Covid-19 patients who have received steroid therapy for covid are particularly at risk of Mucormycosis infection, because steroids suppress the immune system. In a recent study conducted by Garg et al. (2021), 2 out of 3 subjects died due to covid-19 associated Mucormycosis which was diagnosed post-mortem. These patients when discharged from hospitals did not have any other co-morbidities

or risk factors other than being on glucocorticoids during their treatment for covid-19 [37]. Thus, glucocorticoid therapy heightens the risk of Mucormycosis.

### Other immunocompromised patients

Zygomycosis was initially described in Germany back in 1876 when Fürbinger reported the death of a cancer patient whose right lung suffered a haemorrhagic infarct with fungal hyphae and sporangia [39]. During 1980 and 1990 s Mucormycosis was seen in immunocompromised patients [40]. Haematological malignancy is a risk factor in 1–9% of Mucormycosis patients in India, compared to 38–62% in Europe and the United States [5]. A retrospective study carried out at the Children's Cancer Hospital, Cairo, Egypt, during 2007–2017 recorded 3.2 cases/1000 paediatric cancer patient admission, of which 90% of the cases had haematological malignancies [41]. Neutropenia is one of the most common causes of Mucormycosis and this condition mostly exists and persists in severely immunocompromised individuals. There has been a reported rise in Mucormycosis among patients with haematological malignancies, e.g., acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, and in bone marrow transplant recipients due to the neutropenia and immunodeficiency associated with chemotherapy and post-transplant steroid treatment [42, 43]. Furthermore, patients who underwent allogeneic HSCT had more inflammatory cell infiltration compared to non-HSCT patients [44]. Solid-organ transplantation is a risk factor in 2.6–11% of Mucormycosis cases from India, compared to 7–14% from global data. The prevalence of Mucormycosis in renal-transplant recipients in India varies from 0.05 to 2.7%, compared to global data of 0.04–0.05% [5]. Mortality rates for Mucormycosis range from 50 to 80% [45]. There are several other studies that reported Mucormycosis in immunocompromised host suggesting high risk to people with weak immune system and other pre-existing diseases [4, 46].

## Risks of Mucormycosis in immunocompetent patients

Mucormycosis is unusual to affect healthy individuals, but can occur in immunocompetent patients as well. Mucormycosis infection in healthy individuals has a worldwide distribution and the real predisposing factors involved in its pathogenesis in such people are unknown. Some of the possible risk factors in immunocompetent people include occurrence of disease in dark colour people, climatic conditions due to hot weather that could give the chance to causative organism to thrive, air condition which gives organism a great circumstance to multiply, which can further lead for dryness of mucosal epithelium [7]. Low immunity related to poor nutrition, bad hygiene due to socioeconomic poor conditions, surgical procedural related conditions, recurrence of the trauma, poor education, lack of awareness and late diagnosis, are few possibilities as risk factors [47]. Of the risk factors in immunocompetent patients that fosters development of fungal infection includes chronic insult of a well-defined and localized body area [7]. Other reasons includes environmental factors like the hot and humid climate of the country, especially as that seen in India [48]. In addition, unsanitary re-use of face-masks, especially during the prevailing hot and humid weather increases the risk of infection [49].

A study conducted by Sridhara et al. (2005) reported fungal infection in eight healthy individuals. Of the eight cases, three were infected with *Apophysomyces elegans*, again an unusual pathogen causing Mucormycosis [50]. A recent study conducted by He et al. (2021) described the clinical manifestation of a young adult who is immunocompetent but was still diagnosed with Pulmonary Mucormycosis. In addition, they also presented other case studies of immunocompetent patients who were diagnosed with Pulmonary Mucormycosis [51]. Of 14 patients who received antifungal drugs, 6 died due to either respiratory failure or liver failure, accounting to a mortality rate of 43% [52, 53]. The reasons contributing to this might be decompensation of vital organ function which may be a contributing factor to death. However, there are cases where immunocompetent people are also infected with rhino-orbito-cerebral Mucormycosis type of infection and the clinical manifestations of such patients are similar to those occurring in patients with the known underlying conditions [54]. A study conducted by Shivaprasad et al. (2008) described a case of a healthy young male with fungal sepsis secondary to gastrointestinal Mucormycosis [55]. However, reported cases of gastrointestinal Mucormycosis in an immunocompetent host are very few in the literature. Intestinal Mucormycosis is very rare in immunocompetent. Interestingly, a case report described a 40-year-old male patient without any traditional risk factors diagnosed with intestinal Mucormycosis. The patient was cured with aggressive antifungal (parenteral Liposomal Amphotericin B) and supportive care without surgical intervention [56]. Thus, risks of Mucormycosis are not limited to immunosuppressed patients, but immunocompetent people with late diagnosis are also prone to the infection.

## Difficulties in diagnosis of Mucormycosis

Diagnosis of Mucormycosis includes physical examinations and laboratory tests. Lab tests include tissue biopsy and CT scan of lungs, sinuses, or other parts of body depending on the location of the suspected infection. In addition,

diagnostic tools including computed tomography (with prominent halo sign and nodule or mass) and serum polymerase chain reaction (PCR) (detects Mucorales DNA in the serum at an early stage) are efficient tools to diagnose the infection [57]. Molecular based assays are often recommended as valuable add on tools that complement conventional diagnostic procedures. It includes conventional PCR, restriction fragment length polymorphism analyses (RFLP), DNA sequencing of defined gene regions and melt curve analysis of PCR products [58]. A recent study describes new diagnostic tools such as Nano-based sensors which can help early diagnosis and help control the disease. They also discuss about various other nanotechnology approaches such as fungal detection biosensors, nucleic acids-based testing, point-of-care tests, and galactomannans detection for diagnosis of Mucormycosis [59].

Typical signs of Mucormycosis such as blocked nose, fever, breathlessness, vomiting and other similar signs are often mistaken as symptoms of influenza or covid-19. Unfortunately, due to this reason, diagnosis is often delayed. In addition, clinical conditions such as invasion of blood vessels, infarction, thrombosis, and tissue necrosis are exhibited at a later stage of infection and are not readily detectable. Clinical signs and symptoms of Mucormycosis in all kinds of patients is shown in Fig. 3 [60–65]. Currently, in most covid-19 patients, Mucormycosis are diagnosed at the advanced stages of infection increasing the risk of therapeutic failure and mortality rate. Mucormycosis can be fatal in lately diagnosed covid-19 patients due to high risk of failure of treatments and compromised immune system.

In case of immunocompetent patients, routinely used methods include bronchoalveolar lavage culture or histopathologic examination of biopsy of infected tissue and in some cases post-mortem. Imaging techniques and cultures are not totally reliable, hence histopathological examination can be considered as definitive diagnosis method. Differential diagnosis of any severe acute headache, sinusitis, or orbital cellulites should be done with care in case of immunocompetent people. In case of rhino-orbito-cerebral Mucormycosis, there is a high index of suspicion in patients with sinus infections. Especially, if the patient shows worsening course to initial therapies. Some reports have shown that, most of immunocompetent patients with rhino-orbito-cerebral Mucormycosis tend to have delayed diagnosis and management [47]. Similarly, in case of paranasal Mucormycosis, differential diagnosis of paranasal sinus disease (including squamous cell carcinoma of the maxillary sinus) is important and the prognosis is dependent on early diagnosis [66]. Thus, earlier the intervention the better the outcomes and the purpose of all case reports of Mucormycosis

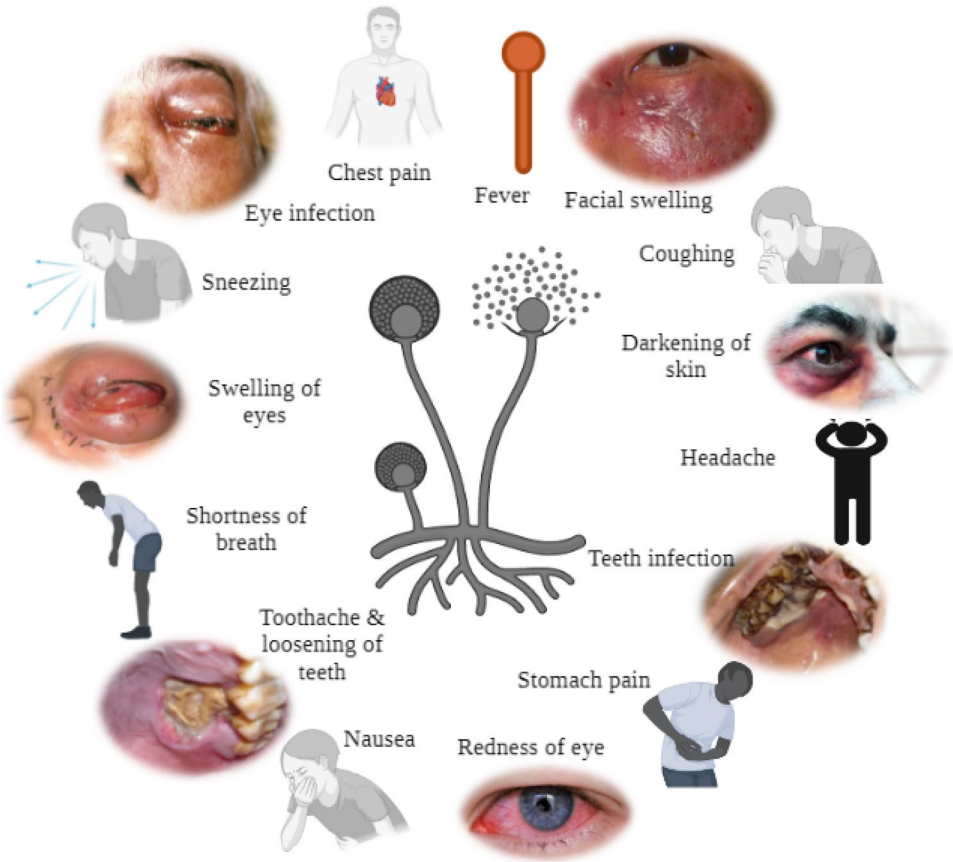


**Fig. 3** Representative clinical signs and symptoms of Mucormycosis in patients. Image Source:[60–65]

in immunocompetent individuals highlight the need for early diagnosis, in addition, differential diagnosis and prompt treatment of this potentially deadly fungal infection.

## Challenges and treatment options for Mucormycosis

Treatment for Mucormycosis includes rapid accurate diagnosis, immediate surgical debridement, and administration of antifungal drugs, recombinant cytokines or transfusion of granulocyte and prosthetic obturator [67]. According to Spellberg et al. (2012) monotherapy showed high mortality rate especially with haematology patients and hence proposed the choice of "Combination therapy" for Mucormycosis [68]. Few years ago, various antifungal drugs were tried to treat the infection, of which few were recommended. First-line of antifungal treatment include Amphotericin B Deoxycholate, Liposomal Amphotericin B (5–10 mg/kg), Amphotericin B lipid complex, Amphotericin B colloidal dispersion, Posaconazole (400 mg bid) and managing of core medical conditions. Second-line treatment includes combination of lipid Amphotericin B and caspofungin, combination of lipid Amphotericin B and Posaconazole [69].

Globally applicable treatment for management of Mucormycosis includes First-line treatment with high-dose liposomal Amphotericin B, isavuconazole (intravenous) and posaconazole (either intravenous or delayed release tablet with moderate strength). Amphotericin B deoxycholate was reported to cause substantial toxicity, and thus is usually not recommended. However, isavuconazole and posaconazole are strongly recommended for salvage treatments [70]. In addition, the guidelines for treatment of Mucormycosis provides recommendations for prophylaxis, secondary prophylaxis, fever-driven and diagnosis-driven treatments [70].

Treatments for immunocompetent patients include surgery followed by Amphotericin B, caspofungin or voriconazole and posaconazole, either alone or in combination. A study conducted by Grimaldi D et al. (2017) showed the benefits of nivolumab and interferon-ϒ in an immunocompetent patient with extensive abdominal Mucormycosis who was initially unresponsive to conventional therapy [71]. However, this combined therapy needs to be tested on larger subjects. Furthermore, treatment against this infection becomes more challenging in case of patients with antifungal drug resistance [70].

In the current scenario, effective treatment for covid-19 associated Mucormycosis should be aimed at early diagnosis, formulation of liposomal Amphotericin B, timely surgical debridement of infected tissue and immunotherapies. Targeted immunotherapies such as cytokine-mediated will help in activating the immune cells of the innate immune response or promote the expansion of Mucorales-specific T cells. However, more studies are required to understand the mechanism of action of different cells against Mucorales. Care must also be taken while treating the patient with immunomodulants, as partial knowledge of immunotherapy can make the patients prone to other secondary infections such as hyperinflammation, anaphylaxis etc.

Currently used treatment for Mucormycosis involves the early initiation of therapy, urgent and complete surgical debridement of infected and surrounding tissue, antifungal therapy, and managing the underlying disease. Preliminary step is surgical debridement has to be extensive, involving all necrotic areas for rhino-oculo-cerebral infection, and repeated surgical procedures to achieve local control and improved outcome [57]. Commonly used anti-fungal agents including fluconazole, voriconazole, and echinocandins do not work against fungi that cause Mucormycosis. For this reason, Amphotericin B (given intravenously), posaconazole or isavuconazole (given intravenously or orally) are currently used drugs for Mucormycosis. Pilmis et al. (2018) described among antifungal agents, the first-line recommended is liposomal Amphotericin B or Amphotericin B lipid complex, and there are no data for the use of posaconazole as first-line therapy [57]. A retrospective study of 41 cases of rhino-orbital-cerebral Mucormycosis showed a survival benefit of patients who were treated with a combination of Amphotericin B with caspofungin [72]. Existing data showed that the mortality rate was low in patients treated with a combination of Amphotericin B and surgical debridement of the infected tissue (19–44%) compared with Amphotericin B monotherapy (50–61%), these findings are in concordance with global data [70, 73]. Further, in majority of the cases urgent surgical debridement to remove the infected necrotic tissue is suggested followed by antifungal therapy. Interestingly, a rare case of delayed-onset gastric Mucormycosis in a polytrauma patient was successfully treated by antifungal medical therapy alone without any surgical debridement [74]. However, the major drawbacks in Mucormycosis management in developing countries are crucial gap in initiation of treatment protocol and the financial constraints of patients to afford liposomal Amphotericin B. Recently, Lactoferrin was being investigated as a potential fungistatic agent and an immune regulator that acts as an iron-chelator [75]. This new approach can be exploited as the adjunct treatment for Mucormycosis infection. Thus, new advances in treatment options are most needed to overcome the drawbacks and to manage Mucormycosis.

## Precautions and care to manage Mucormycosis

Mucormycosis can be fatal as they are categorized by rapid progression. With the current knowledge, it is known that there is a high risk of Mucormycosis in covid-19 patients.

Thus, we suggest some of the precautions and care that help in effective management of Mucormycosis in covid-19 patients. Firstly, blood glucose level must be regularly monitored in post-covid-19 discharge patients including both diabetic and non-diabetic patients. Detection of Mucormycosis by radiological or molecular assays in covid-19 admitted patients should be a routine procedure. With the current knowledge of the risks of Mucormycosis in covid-19 patients, doctors suggest early detection and crucial time to initiate treatment for Mucormycosis is a key to fight the disease. They suggest any alarming signs and symptoms should never be neglected. One such example is, neglecting cases with a blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/or Covid-19 patients on immunomodulators. Unfortunately, as we are seeing rising deaths of covid-19 associated Mucormycosis patients, the situation could turn devastating with mortality rate of 100% if health, symptoms and hygiene is not critically monitored.

Nevertheless, any symptoms should never be neglected in immunocompetent patients and timely diagnosis and initiation of treatment can help in reducing morbidity and mortality in healthy individuals. However, some types of Mucormycosis possess great difficulties in identification, such as pulmonary Mucormycosis which represents clinical presentations that are difficult to identify. Thus, clinicians should bear in mind that even immunocompetent people are prone to any type of Mucormycosis infection by reviewing the exposure history. Moreover, clinicians should be cautious with the occurrence of pulmonary embolism in patients with signs of lung infection [51]. Mucormycosis in immunocompetent individuals can be effectively managed by maintaining good nutrition in diet, good hygiene, thoroughly sterilizing air, water, oxygen supply, equipments used for surgical procedures, educating public about precautions, care and creating awareness about disease and most importantly early diagnosis (without any negligence as in case of healthy individuals) and timely treatment.

In addition, in people who have received organ transplant or stem cell transplant, who are at high risk of infection need to contact clinician and take prescribed antifungal medication to prevent Mucormycosis. Timely treatment and choice of therapy can greatly impact its success. In current covid-19 pandemic, there are still trials going on to treat covid-19 patients, but for extremely ill patients, steroids are one of the treatment options. Steroids which are life saviours for covid-19 patients should not be used unless absolutely necessary. It is suggested to stop continuing immunomodulating drugs and in addition, steroids should be used judiciously, and correct dose of the same must be given at right point of time. However, it is challenging to take a decision if a patient was already on steroids even before getting infected with covid-19. Thus, more studies need to be carried out on different populations to treat such cases in order to prevent Mucormycosis infection.

There are multiple ways we can prevent this infection in covid-19 patients. Firstly, the hospital and critical care wards should be kept clean and regularly checked for spores in air. Secondly, humidifiers used during oxygen therapy should be sterilized thoroughly. Thirdly, on-time diagnosis of symptoms and treating the patients without any delay. Fourthly, requesting the discharged covid-19 patients to stay at home and avoid direct contact with soil or dust for at least 14 days until they regain their natural immunity and strength. Recently, a study conducted by William et al., showed that careful design and evaluation of heat, ventilation, air conditioning systems minimized the airborne transmission risk of Mucormycosis and covid-19 infections in hospital environment. They showed that, Dedicated Outdoor Air System model reduced the $CO_2$ emissions to 691 tons, with a potential of reducing heating, ventilation, and air conditioning and whole-building energy use by 37% and 16%, respectively in the hot arid climate, with a return on investment of about 6% [76]. Another recent study by Soltan et al., demonstrated the first ever developed multitope vaccine against Mucormycosis causing fungi based on the immunoinformatic approach [77]. Thus, proper precautions and care in patient health and maintenance of hygienic and controlled environment are necessary to manage Mucormycosis effectively.

## Conclusions

Mucormycosis is highly aggressive and is alarming due to its increasing morbidity and mortality rate. Diagnosis of this disease is often difficult due to the misinterpretation of signs and symptoms with other diseases, especially covid-19. In addition, the clinical manifestations of the disease often delay its diagnosis at the late stage. Delayed diagnosis directly affects the treatment protocol and often leads to failure of the treatment due to rapid spread of infection in the body that not only destroys immune cells, but also becomes unresponsive to medicines. Mucormycosis affects immunocompromised patients including diabetes, haematological malignancy, organ and skin transplant and covid-19 patients. Moreover, covid-19 patients who have received steroids for covid are particularly at high risk of Mucormycosis infection, as steroids suppress the immune system. Mortality rate was reported 90% or even more with Mucormycosis in case of diabetes and 50–80% in case of covid-19 patients. Importantly, Mucormycosis is also reported in immunocompetent individuals, which is a great cause of concern and necessitates quick attention. However, Mucormycosis can be prevented in healthy individuals by good hygiene and nutrition and can be treated with proper and timely diagnosis. Globally

applicable treatment for management of Mucormycosis includes surgical debridement of infected tissue followed by first-line treatment with high-dose liposomal Amphotericin B, in addition isavuconazole and posaconazol are also prescribed.

## Future perspectives and research directions

Covid-19 associated Mucormycosis can be effectively managed by monitoring air for spores, adequate sterilization of air and equipments (especially humidifiers used during oxygen therapy) in hospitals, routine diagnosis for Mucormycosis in all covid-19 admitted patients, urgent surgical debridement of necrotic tissue, combined antifungal therapies, judicious use of steroids, reduced use of immunomodulating drugs, implementing combinations of immunotherapies and advice of at home stay for post-covid patients until they regain immunity and strength. Additionally, diagnosis and treatment of Mucormycosis should be considered on population-based methods in different set of populations (due to variation in medical history), across different countries, due to the fact that different organisms are involved in causing the disease (variation in clinical manifestations in different forms). Prospective validation, similar studies of other populations at risk for Mucormycosis and development of a "scorecard" for diagnosis of Mucormycosis is suggested. In addition, molecular tools with improved definition of the clonality of Mucormycosis cases is required which can give more insights on epidemiology of Mucormycosis. Further, more research and clinical trials needs to be carried out to develop drugs or combination therapies for successful treatment of Mucormycosis. Moreover, since the estimated prevalence of Mucormycosis is around 70 times higher in India than that in global data and the exact incidence of this is unknown especially due to the lack of population-based studies, extensive awareness of the disease and precautions are crucial to manage Mucormycosis in the current Covid-19 pandemic.

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