An emergence of mucormycosis during the COVID-19 pandemic (Review)

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Abstract. Mucormycosis was highly prevalent during the coronavirus disease 2019 pandemic, particularly during the second wave, causing increased health risks to immunosuppressed or compromised individuals. This infection is long-standing, lasting for years, specifically in immunocompromised individuals. There are no apparent risk factors and the fungus affects skin/subcutaneous tissues, resulting in the loss of facial aesthetics. In addition, individuals with a hyperglycaemic condition or diabetes mellitus, the fungus can lead to more severe complications, which are often fatal. While in patients with diabetic ketoacidosis, a high risk of infection with *Rhizopus oryzae* is observed, with the production of ketoreductase; this enzyme in turn hydrolyses host ketone bodies. Relatively effective medications are becoming available; however, the prognosis of patients affected by this fungus may improve with an increase in awareness and early diagnosis with the intervention of expert surgeons, radiologists and microbiologists to effectively combat the condition. The present review discusses the types, symptoms and available treatment strategies for mucormycosis.

Contents

1. Introduction
2. Parallelism of COVID-19 and mucormycosis
3. Clinical classification of mucormycosis
4. Epidemiology
5. Symptoms
6. Aetiology and pathophysiology of the fungus
7. Conditions such as diabetes and the incidence of mucormycosis
8. Diagnosis
9. Prophylaxis and treatment
10. Comorbidity effects of mucormycosis
11. Preventive measures
12. Conclusion and future perspectives

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1. Introduction

Following the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the incidence of mucormycosis has increased. This, in conjunction with the pandemic has caused devastating human health issues globally, particularly among South Asian and other Asian countries, particularly in individuals with major predisposing conditions, such as uncontrolled diabetes mellitus, comorbidity effects from steroid therapy with elevated iron levels (1). Mucormycosis can be defined as an angio-invasive fungal infection with relatively high morbidity and mortality rates. Broadly the species of the phylum Zygomycota cause mucormycosis, particularly Mucorales and Entomophthorales. In Mucorales, four genera that are most closely associated are *Cunninghamella, Rhizopus, Mucor, Absidia*, etc. *Conidiobolus* and *Basidiobolus* are the two key genera belonging to the Entomophthorales order and tend to cause infections in human beings (2). The etiologic agents of mucormycosis are cosmopolitan in distribution. The mucormycosis condition is a classical opportunistic invasion and typically affects immunocompromised individuals, particularly those with conditions, such as ketoacidosis, burn or trauma, or those under iron chelation treatment and some individuals who are severely immunocompromised due to malignancy or even chemotherapy (3). The case incidence of mucormycosis is underrated possibly due to laborious diagnostic procedures and mostly depends on histopathalogical analysis or the culturing process and remains under-reported (4).

Among all mucormycetes, *Rhizopus oryzae* is the most widespread strain and contributes for 60% of human cases and is also responsible for 90% of rhinocerebral mucormycosis cases (5). With a devastating and multifaceted clinical symptomatology, mucormycosis has emerged as an infectious disease worldwide. *Mucor* moulds are generally found in soil, plants, manure or even in fruit and vegetable compost, and are rarely found in air as a transient existence. Depending on the site of infection, mucormycosis differentiates into a

rhinocerebral, pulmonary, cutaneous and gastrointestinal infection (6). The pathogenicity of infection ranges from mild to fatal, depending on the incubation period of the moulds. The incubation period of this fungus is 5 to 6 days; individuals can become infected by inhaling spores of moulds. Mucormycosis is generally non-contagious, and due to potential innate immunity, the majority of individuals exposed to the spores do not develop infection (7).

Once affected by Mucorales, the disease progresses rapidly. Moreover, opportunistic fungi, such as *Mucor irregularis* or *Rhizomucor variabilis* reported from China, tend to cause diverse epidemiological and clinical manifestations (8).

2. Parallelism of COVID-19 and mucormycosis

In India, ~31 million individuals were affected by the COVID-19 pandemic, and the number of COVID-19-related mucormycosis cases also simultaneously increased, particularly during the second wave, which occurred in June, 2021. During 2021, mucormycosis was observed to be prevalent in India, and its estimated incidence was 14 in every 100,000 individuals compared to other cases (9). A sudden emergence of mucormycosis cases along with COVID-19 was observed; although rare, mucormycosis was a serious and rapid complication associated with COVID-19 (9). The major cause of this condition was Mucorales spore inhalation by patients with COVID-19 with a low oxygen (hypoxia), hyperglycemic index or even steroid-induced hyperglycaemia, acidic conditions such as metabolic acidosis, diabetic ketoacidosis and high iron levels (increased ferritins), with a decreased phagocytic activity of white blood cells (WBCs) due to immunosuppression (SARS-CoV-2-mediated or other comorbidities). This was coupled with prolonged hospitalization with or without COVID-19 infection or sometimes after a few weeks of recovery (5-9). However, during the COVID-19 pandemic, the number of mucormycosis cases increase in India perhaps due to improper hygienic maintenance in hospital linens, medications and packaged foods. This increase may also be due to the following reasons: Following infection with COVID-19 patients have a low immune status due to a decrease in WBCs. In addition, during the viral infection, patients are medicated with corticosteroids and tocilizumab to reduce lung inflammation, which often worsens the immune status, hence leading patients to become prone to fungal infection (9). The extent of acute *Mucor* infection is dependent upon the overall immunological status and overall health status of an individual. As COVID-19 can damage respiratory tissues and blood vessels, this increases the susceptibility to fungal infection; black fungus invades (angioinvasive mycosis) rapidly and multiplies in blood vessel walls where it effectively reduces and tears blood vessels and tissues, thereby resulting in tissue damage (10). The infection can have adverse affects in oxygen-dependent patients with poor sanitary or aseptic practices.

3. Clinical classification of mucormycosis

Depending on the site of infection, mucormycosis may be categorised into the following types (Table I).

Rhino-orbito-cerebral mucormycosis (ROCM). ROCM is the most common clinical manifestation of mucormycosis. The infection begins with the inhalation of spores, spreading into the paranasal sinuses (11). The primary etiological agent of ROCM is an aseptate fungus (*Rhizopus oryzae*) which is associated with a 50% mortality rate. The fungus proliferates to adjacent tissues such as the palate, sphenoid sinuses, orbits or cavernous sinuses and enters the central nervous system. Black eschar is the necrotised tissue patches due to the local extension of fungal invasion (12).

Pulmonary mucormycosis. This infection is typically associated with haematological malignancies [Centers for Disease Control and Prevention (CDC) guidelines] (13), mainly associated with the lungs and is the dominant form of mucormycosis observed in patients with transplantation or in immunocompromised individuals (14). In the majority of cases, symptoms are generally non-specific and may include fever, cough, dyspnoea and chest pain. The infection presents with typical lesions involving parenchyma cells may extend to various sites in the cardiac regions (11,14) with the causative agent is *Rhizopus* or *Mucor.*

Cutaneous mucormycosis (CM). CM may be classified into primary and secondary. Primary infection occurs by the direct introduction of fungal spores to damaged skin, whereas secondary infection occurs through dissemination from previously infected regions, such as through rhinocerebral infection (15). *Apophysomyces elegans, Lichthemia* and *Mucor* spp. are the main Mucorales species involved in primary CM, which accounts for necrosis, redness, swelling, purulent discharge and a mouldy appearance over the skin. The secondary infection is acute with a high mortality rate. Initial symptoms include sinusitis with necrotic eschar and the further loss of vision, as well as other neurological deficits (16).

Gastrointestinal mucormycosis (GIM). Primary GIM is the less frequent form of the disease. GIM results due to the consumption of contaminated food, such as dried contaminated bread or bakery products in addition to contaminated medical devices (11-17). In the gastrointestinal tract, the stomach is the first target site of infection and this may lead to infection in the colon and later to the ileum, as well as to the duodenum and jejunum (17). Gastrointestinal bleeding with altered bowel habits and severe abdominal pain are the typical symptoms (18). The causative agent of GIM is typically *Mucor* and precipitated with *Aspergillus* and even *Salmonella* infection.

Disseminated mucormycosis (DM). DM involves at least two non-contiguous sites, commonly infecting the lungs/sinus/soft tissues/central nervous system/liver/kidneys (19) mainly by *Mucor* and other zygomycetes. A high iron concentration and profound immunosuppression are the main predisposing factors for DM. Shirane *et al* (20), through a case study analysis on a 58-year-old male patient revealed that the autopsy result of the patient's body disclosed the presence of *Mucor* in heart, liver, right kidney, right adrenal gland and cerebellum, which resulted in thromboangiitis and infarction in these organs.

Table I. Types of mucormycosis and the associated risk factors and symptoms.

Clinical forms of mucormycosis	Risk factors	Symptoms	(Refs.)
Rhino-orbito-cerebral mucormycosis (ROCM)	Diabetes, solid organ transplant, corticoster -oid therapy, chronic kidney disease and intravenou -s drug usage	Fever, Headache, Facial swelling, Facial pain, Nasal discharge, Epistaxis, Sinusitis, Hemipleagia	(1,23-28)
Pulmonary mucormycosis (PM)	Haematological malignancy, diabetes mellitus, haematopoietic stem cell transplant or organ transplant, renal disease in PM, post pulmonary tuberculosis	High fever, persistent cough, pleuritic chest pain, dyspnoea and haemoptysis.	(26-31)
Cutaneous mucormycosis (CM)	Immunocompetent patients, diabetes mellitus, SOT, penetrating trauma, open wound trauma/motor vehicle accident/surgery, contaminated surgical dressings/burns/natural disasters/animal bites or scratches	Localized infections restricted to cutaneous and subcutaneous infections, Fungal invasion to muscles, bones and tendons/ necrotising fasciitis	(26,27, 32,33)
Gastrointestinal mucormycosis (GM)	Patients with malnutrition or undergoing peritoneal dialysis, solid organ transplant patients, haematological malignancies and neutropenia, diabetes mellitus, chronic alcoholism, the administration of broad-spectrum antibiotics	Abdominal pain, gastrointestinal bleeding, abdominal distension and diarrhoea	(27,35,36)
Renal mucormycosis (RM)	Kidney-associated diseases, dialysis.	Fever, flank pain, haematuria or anuria	(33,37-40)
Disseminated mucormycosis (DM)	Solid organ transplant and haematological malignancy patients	Spreading through blood, leading to brain/sinus/lung/central nervous system/liver and or kidney infection	(26,41)

Uncommon presentations. Uncommon presentations include endocarditis/bone or and joint infections/peritonitis/pyelonephritis. Osteoarticular mucormycosis may affect after the trauma/surgical process. Peritonitis occurs due to continuous ambulatory peritoneal dialysis, while isolated renal mucormycosis is commonly observed in patients with intravenous drug usage or renal transplant patients. Another significantly rare manifestation is isolated cerebral mucormycosis, involving the central nervous system following proliferation from the paranasal sinus (21).

Health-care associated mucormycosis (HCM). HCM is a matter of utmost concern, particularly in neonatal units, haematology, the transplantation of grafts or even in intensive care units, diabetes and severe prematurity (3). Surgical intervention is associated with 41% of HCM cases, while other cases are linked to the use of contaminated medical devices, such as adhesive bandages/tongue depressors/ostomy bags or others (21).

4. Epidemiology

The number of COVID-19 pandemic-associated black fungus infection cases has increased globally and a similar situation was observed in India. Furthermore, In India, The National COVID-19 task force has issued an advisory notice and the Union Health Ministry has instructed the states/UTs to declare black fungus as an epidemic. Infection with Mucorales, particularly in immunocompromised individuals can be quite rampant and progressive with the etiological agent being the opportunistic fungus, *Mucor irregularis* (22). Generally, the infection is chronic, occurring in immunocompetent patients, involving the skin and subcutaneous tissues, leading to severe complications. In India, the state of Rajasthan first declared a mucormycosis epidemic, while the city of Surat noted that 8 out of 40 COVID-19 survivors developed this infection in the eyes and lost their vision (information obtained from the India Today web desk during the second lockdown in 2021) (22).

5. Symptoms

Mucormycosis symptoms generally begin with sinusitis, nasal blockage, congestion with blackish or bloody nasal discharge, pain in the cheek bone or one-sided facial pain, numbness, swelling, blackish discoloration on nose palate, loosening of the teeth, blurred or double vision with pain, thrombosis, necrosis, chest pain, pleural effusion with difficulty in respiratory functions (21-41) (Fig. 1).

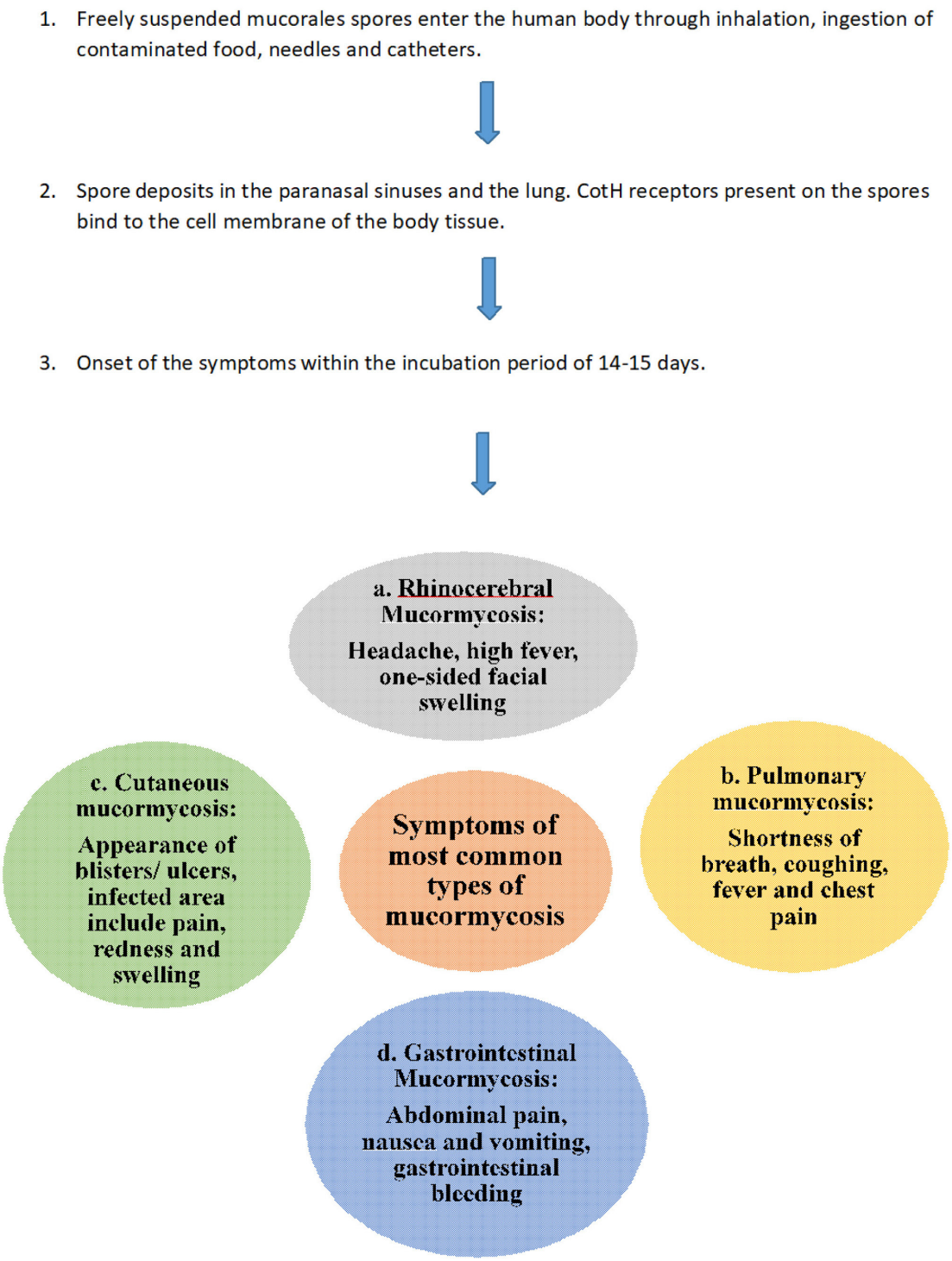

Figure 1. Pathogenisis and symptoms associated with most common types of mucormycosis.

6. Aetiology and pathophysiology of the fungus

The word mycosis stands for the lethal fungal disease caused by infection and direct interaction of fungal spores with the body tissues. Mucormycosis, dermatophytoses, yeast infections, systemic mycoses and mycetoma are the pathogenic fungi involved in mycosis disease (42). Prakash *et al* (43) documented the pathogenic Mucorales fungi, *Rhizopus*, *Lichtheimia*, *Cunninghamella*, *Rhizomucor* and *Apophysomyces* as the causitive agents of mucormycosis, which were isolated from Indian soils and similarly from air samples. Among the *Rhizopus* species, *Rhizopus arrhizus* and *Rhizopus homothallicus* are the most common agents causing ROCM. *Apophysomyces variabilis* is the second highest causative agent and accounts for 60% of the total cases of mucormycosis in the population (44). During the COVID-19 pandemic, the main factors responsible for the development of COVID-19-associated mucormycosis included the high rate of diabetes mellitus, unsanitary/poor hygienic conditions and high ferritin levels in the body (45). The disease sets with

the entry of *Mucor* or other strain spores via the air tract either through the nose, mouth or skin lacerations (46). Upon the entry of the spores, individuals who are compromised with cellular and humoral immunity are unable to provide a defence against the pathogen (47). Thus, the fungus can then spread to the paranasal sinuses, and later to the orbit, meninges or brain. Angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS-2) are the two receptors through which COVID-19 enters the cell. ACE2 is the receptor for the majority of cells in the body and has a higher rate of expression in the respiratory and renal tract, and gastrointestinal epithelium. TMPRSS receptors are similar to ACE2, but are present only in respiratory and gastrointestinal epithelial cells. TMPRSS-2 along with ACE2 receptors has a tendency to attack lymphocytes, thus reducing $CD4^+$ and $CD8^+$ T-cell counts, resulting in a weaker immunity, also inducing lymphopenia. The reduction in the T-cell number consequently increases interleukin levels and effectively achieves the state of the cytokine storm (48). The cytokine storm weakens the defence system reserve pool, causes the atrophy of lymphoid tissue, and prevents the further production, differentiation and proliferation of protective lymphocytes. The weakened immune system paves the way for the entry of Mucorales into the body. Another key condition which fuels the fungal growth is lactic acidosis; this eventually destroys type II alveolar cells, leading to excessive respiratory disabilities that intensify acid-base levels. The resulting hypoperfusion and hypoxemia worsens the condition of the body by increasing acidic conditions. The coupled reaction of the cytokine storm and lacto/keto acidosis aggravates the state of the patient; in this case, there is an urgent need for treatment through immunosuppressive steroids. These criteria promote an ideal environment for the fungus to grow (49). In addition to this, increased ferritin level due haemolysis and an increased body temperature promote the growth and development of the fungus in immunosuppressed individuals (50). The ACE2 receptor nourishes the growth of Mucorales by damaging pancreatic β-cells, which results in elevated plasma glucose levels, and the consequent increase in glucose levels feeds the fungus. This explains the increased rate of mucormycosis in diabetic patients (6,47,48). These irreversible consequences eventually deteriorate the overall health status of the patient, often leading to fatal results (51).

7. Conditions such as diabetes and the incidence of mucormycosis

It has been reported that during 2013-2015, in four major tertiary care hospital in India, there were 388 incidents of mucormycosis, and 56% of these cases had unregulated diabetes, which demonstrates that the existence of underlying conditions predisposes the proliferation of the fungus. In addition, trauma was reported in 10% of these cases, which signifies the linkage of this fungal infection to diabetes (39,41,52). India has a prevalence of diabetes of 9% in the adult population (44). Conversely, coronavirus infects the pancreas and can disrupt blood sugar levels perhaps due to the infection or due to clinical treatment. In this context, host immunity appears to be compromised; consequently, elevated sugar levels provide an ideal pabulum for mucormycosis development and in individuals with uncontrolled diabetes, this enables the highest replication of SARS CoV-2, which produces mitochondrial reactive oxygen species and activates hypoxia-inducible factor 1α (18,19). In fact, the uncontrolled diabetes condition enhances acidic media, which is an ideal condition for the proliferation of the fungus. Thus, mycelial invasion and proliferation are promoted by the hyperglycaemic index and acidosis (53) followed by the enhanced release of iron from ferritin (due to acidosis). Therefore, it is critical to maintain blood sugar levels under control during the course of antifungal treatment.

In a case study conducted among 95 patients with COVID-19-associated mucormycosis (CAM) who were admitted to the Bowring and Lady Curzon Hospital from June to September, 2021 (70 males and 25 females), 69% of the patients had type 2 diabetes mellitus with mean serum ferritin levels of 537.38±468.88 ng/ml. The patients were positive for Mucorales and the KOH test, while serum ferritin levels were markedly elevated and identified as *Aspergillus*, *Mucor*, *Rhizopus* and *Candida spp.* (54).

8. Diagnosis

Since the mortality, morbidity and haematological defects are prominent features, the diagnosis of mucormycosis poses a tough challenge. Rapid diagnosis from invasive aspergillosis is of top priority as antifungal treatment would differ, while the underlying clinical conidtions are almost similar (6,55). Basically, direct microscopy was the gold standard for diagnosis until recently; however, the process was cumbersome. In the case of invasive aspergillosis, the assay for circulating antigens, such as galactomannan/β-D-1,3-glucan is ideal, although it provides no evidence of Mucormycosis (56). Hence, for mucormycosis, direct microscopy, histopathology for hyphal detection and invasion along with the analysis of cultural characteristics on Sabouraud dextrose agar or potato dextrose agar are optimal diagnostic tools. With the advent of molecular biology tools and applications, the rapid detection of fungal infection has become a reality. A quantitative multiplex polymerase chain reaction (qPCR)-based 18S rRNA targeting *Mucor*/*Rhizopus, Lichtheimia* and *Rhizomucor* has recently become a hallmark of detection, particularly during the early stages and even within 3 days of the disease onset using blood or serum with 90% authenticity (52). In the case of post-burn infection, this can be detected 11 days before standard diagnosis. RT-PCR analysis of Mucorales in tissue/biopsy for haematological malignancies can detect probable mucormycosis infection (57).

9. Prophylaxis and treatment

The effective treatment of mucormycosis is generally based on a multifaceted strategy, which may include early medication at the optimal dosage, the complete evacuation of the fungus and use of diverse adjunctive therapies (58). The majority of Mucorales exhibit resistance to most antifungal agents *in vitro* (voriconazole). Amphotericin B is an effective drug, with the exception of some species of *Cunninghamella* and *Apophysomyces* (6). In addition, posaconazole and isavuconazole are also effective, and itraconazole and terbinafine exhibit some activity against certain species.

Amphotericin B. The recommendations from the European Conference on Infections in Leukemia (ECIL-6) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/European Confederation of Medical Mycology (ECMM) guidelines suggest the usage of a lipid formulation of amphotericin B as a frontline therapy (59).

The liposomal amphotericin B suggested dose is 5 mg/kg/day and the maximum 10 mg/kg/day (central nervous system infection). Amphotericin B is the polyene antifungal agent (highly protein bound and poorly dialyzable) and binds to sterols (ergosterol) on the fungal cell membrane surface. This antifungal drug change in membrane permeability leading to cell cytoplasmic leakage. The high dosage of this antifungal drug can result in chills, fever, phlebitis, renal damage and anaphylaxis as side-effects. Dosage may gradually increase from 5 to 10 mg/day, up to a total dose of 0.5 to 0.7 mg/kg/day, depending on the cardiorenal status of the patient. An important risk factor while using amphotericin B is that the dosage must not exceed 1.5 mg/kg; an overdose can result in cardiorespiratory arrest (60). A new formulation, namely a lipid complex (amphotericin B) was designed, as it is less nephrotoxic than the existing amphotericin B. This lipid-based formulation increases the retention time during circulation and alters the biodistribution. The amphotericin B complexed with lipid concentrations induces capillary permeability in body tissues, as normal tissue is purely impermeable to lipid-complex drugs. This method of increasing the localization of drugs in the targeted sites is termed passive targeting. This method enhances drug delivery to the fungi in infected organs and phagocytes with a lower toxicity, while maintaining antifungal efficacy with drug levels sustained in tissues with the action of lipase for drug release (61). The suggested dose for liposomal amphotericin B is 5 mg/kg/day minimum to as high as 10 mg/kg/day (central nervous system infection).

Mechanisms of Amphotericin B. The antifungal drug amphotericin B, a macrolide, derived from *Streptomyces nodosus* which acts upon the plasma membrane of the fungi (62). This antibiotic molecule binds to the sterols present in the plasma membranes, such as ergosterol of fungal cells and cholesterol of mammalian cells. It has a higher affinity towards ergosterol than cholesterol (63). Amphotericin B enters through the cell wall of the fungus and binds to the ergosterol present on the plasma membrane. This creates an ionic imbalance by forming pores, and leads to the leakage of potassium ions from the hydrophilic ion channels created inside the fungal membrane. Amphotericin B has a high binding affinity towards potassium ions and is hence known as an ionophore. The leakage of potassium ions causes the loss of membrane rigidity, resulting in the discharge of essential small molecules from the membrane; through this manner, amphotericin b exhibits its fungicidal activity (64). The mechanisms of action of amphotericin B are illustrated in Fig. 2.

Triazoles. Triazoles are currently in clinical use and are the largest class of antifungal drugs. Out of the 40 second-generation triazoles, posaconazole and isavuconazole are two key antifungals that possess good activity against Mucorales. The mechanism of drug action involves the inhibition of the 14-α demethylation of lanosterol present in the ergosterol biosynthetic pathway. The demethylation of lanosterol results in the depletion and the replacement of ergosterol with toxic 14-α-methylsterols, thus altering membrane permeability and inhibiting membrane-bound enzymes (65).

Posaconazole. Posaconazole is similar to itraconazole in its structure, considered as second-line or salvage therapy for patients who are intolerant to amphotericin B (66). Isavuconazole is structurally resembles fluconazole, and is the only antifungal drug approved for use in the treatment of invasive mucormycosis. At present, isavuconazole is available in the market in its prodrug form known as isavuconazonium sulfate, which is rapidly metabolized by serum butylcholinesterase to its active form. The recommended dosage for the intake of isavuconazonium sulfate is 372 mg every 8 h for six doses, and 372 mg daily (67). *In vitro*, isavuconazole exhibits activity against *Lichtheimia*, *Rhizopus*, *Mucor* and *Cunninghamella* spp. (68).

When the fungal infection is at very severe stage, surgical intervention is the only alternative. In this context, necrotic tissues have to be removed along with surrounding infected healthy-looking tissues to prevent the further proliferation of Mucorales hyphae. Surgery is compulsory during rhino-orbitocerebral infection and soft tissue infection, even in the case of a single localized pulmonary lesion, but has to be carefully considered when infection is disseminated or reaches difficult-to-reach organs.

Ayurvedic and Unani system for the treatment of mucormycosis. Some patients who have recovered from COVID-19 continue to have post-COVID-associated conditions, including mucormycosis. The shortage of medicine creates a vital problem for the treatment of the disease. Hence the research experts from the Ministry of Ayush have asserted the implementation of the Ayurvedic and Unani systems of medicine to prevent the spreading of black fungus (69). Adluri and Perugu (70), following the decision made by the Telangana Government to implement Ayurvedic medicine in the treatment of mucormycosis, assessed the safety and efficacy of the Ayurvedic regime. In Ayurvedic medicine, mucormycosis was termed as Vataja viradhi, and to cure the disease they used Pancha Tkita Ghrita Guggullu (PTGG) as an Ayurvedic adjuvant therapy. They performed controlled palcebo trials for patients with post-COVID mucormycosis in the Gandhi Hospital, a large Government tertiary centre in Telangana. In their case control study, they included 77 patients with post-COVID mucormycosis. A total of 65 patients received PTGG: 36 patients received PTGG for 34.1 days (group 1) and group 2 (n=29), used as the control (dropouts) received PTGG only for 2.1 days. All patients were examined for disease progression, disease recurrence, the persistence of symptoms and mortality before and after treatment (70). The outcomes of the treatment were fruitful with a zero mortality rate in group 1, whereas 13.8% severity was noted in group 2; that case study reported that the use of PTGG was helpful, safe and well-tolerated with concomitant antifungal usage (70). Mohsina *et al* (69) listed some of the Ayurvedic medicine rituals, such as kasaya tikta rasa prayoga, rikta prasadanam, ojo vrddhi krmighna, kapha pitta haram and ruksa. They used many aragvadadi kasayam, amrtottaram kasayam, guducyadi kasayam, nimbadi

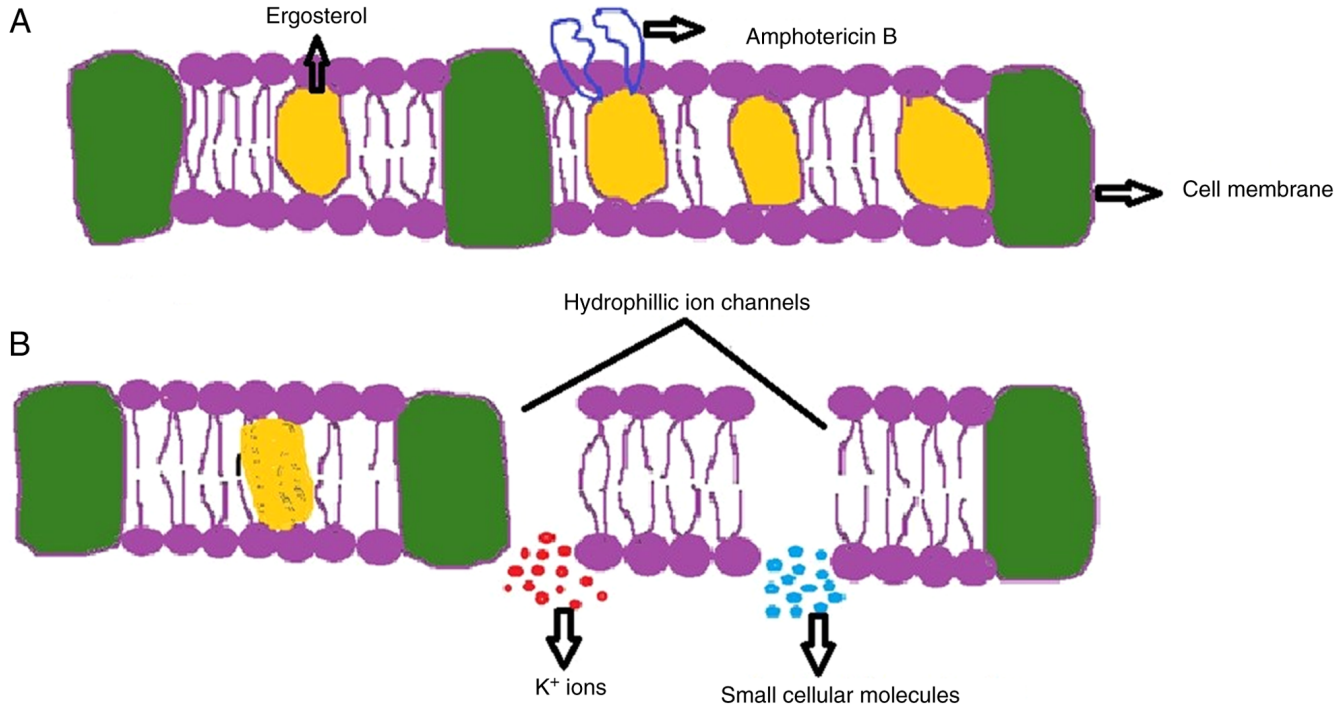

Figure 2. (A and B) Schematic illustration of the mechanisms of action of amphotericin B.

kasayam, sonitamrtam kasayam and katakakadiradi kasayam to treat patients with post-COVID mucormycosis. Visa vilvadi gulika comprised of Bilva, Tulasi, Karanja, Tagara, Devadaru, Marica, Daruharidra, Ajamutra, Haritaki, Vbhitaki, Amalaki, Sunti, Pippali, Haridra, Pathya, Nilini and Isvari. They offered these kashayam at 50, 50, 50 ml on an empty stomach, after food in the morning and before food and finally concluded that these Ayurvedic medicines boost the immunity of patients with post-COVID-associated mucormycosis (69). The leaf extract of *Catharanthus roseus*, *Lantana camara*, *Nerium indicum*, *Sida cordifolia* and *Ziziphus mauritiana* was examined against *Mucor circinelloides in in vitro* antimycotic studies. The highest antimycotic activity was exhibited by the ethanol leaf extract of *Catharanthus roseus,* followed by *Nerium indicum* and *Lantana camara*. *Ziziphus mauritiana* exhibited moderate activity against *Mucor circinelloides* (71). Balakrishna *et al* (72) implemented Anu taila to cure mucormycosis; Anu taila is comprised of tej patra, vidang, nagkesar, chandan, tavak, bala, yeshtimadhu and daru haldi. The consumption of Anu taila improved the immune response against Mucor spores by activating pre-treated human THP-1 cells and TNF-α. The repeated application of Anu taila significantly reduced the ergosterol content in the Mucor biomass and was more effective than amphotericin B, where the replacement of hyphae, sporangiophores and sporangia with the fused biomass was evidently proven in SEM images. Anu taila downregulated the sterol-c5-desaturase coding ERG3 gene, crucial for maintaining structural integrity in *Mucor* spp. and also blocks ergosterol biosynthesis (72).

10. Comorbidity effects of mucormycosis

Mucormycosis may result in the loss of the upper jaw or even sometimes the eyes. Due to this loss of the jaw, patients may have difficulty with chewing, swallowing, facial aesthetics and can suffer a disrupted self-confidence (73).

11. Preventive measures

The early, effective and rapid diagnosis/administration of suitable effective drugs, the application of hyperbaric oxygen, recombinant cytokines, the transfusion of granulocytes, surgical intervention, prosthetic obturator are the typical and crucial methods in successful management (16,74). Patients with uncontrolled diabetes require rapid corrective measures for metabolic abnormalities; the use of sodium bicarbonate (with insulin) is mandatory to reverse ketoacidosis, as it reduces the ability of Mucorales invasion (74). However, the use of immunosuppressive drugs/corticosteroids need to be reduced to the lowest possible level with epidemiological knowledge (75).

12. Conclusion and future perspectives

The COVID-19 pandemic has increased the risk of infections worldwide due to the lack of specific treatments available for the most devastating viral infections. During the second wave of the pandemic, the number of deaths rapidly increased and reached uncontrollable levels. The management of COVID-19 led to the continuous use of steroids, antibiotics and breath supportive sources, such as oxygen carriers and ventilators; these worsened the conditions of patients by increasing comorbidities. Co-morbidities, such as diabetes and cardiovascular diseases intensified during the management of COVID-19, which led to the development of secondary infections, such as mucormycosis. Mucormycosis is an invasive fungal infection accompanied by ketoacidosis, high glucose and high ferritin levels, neutropenia and a lower

immunity. All these parameters make patients immunocompromised, with decreased levels of WBCs, T-cells and other immune cells, leading to a cytokine storm in the body and the impairment of cellular organs. As the management of the disease is critical, novel diagnostic and treatment strategies are required for mucormycosis in order to prevent higher morbidity and mortality rates. Hence, additional extensive research and investigations to elucidate the root cause of mucormycosis are warranted in order to provide clinicians with the tools to combat infection in association with the pandemic.

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Authors' contributions

DG conceived the study and was also involved in the editing, reviewing and revising of the manuscript, and also communicated the manuscript to the journal. RS drafted the manuscript, obtained the data acquired for the review and processed the figures. Both the authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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