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REVIEW ARTICLE

Focusing COVID-19-associated mucormycosis: a major threat to immunocompromised COVID-19

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Abstract

COVID-19 disease has been identified to cause remarkable increase of mucormycosis infection cases in India, with the majority of cases being observed in individuals recovering from COVID-19. Mucormycosis has emanated as an outcome of the recent COVID-19 pandemic outbreak as rapidly developing fatal illness which was acquired by Mucorales fungus which is a subcategory of molds known as mucormycetes. Mucormycosis is one of the serious, sporadic mycotic illnesses which is a great threat to immunocompromised COVID-19 patients and affects people of all ages, including children with COVID-19 infections. This is associated with tissue damaging property and, therefore, causes serious clinical complications and elevated death rate. The COVID-19-associated mucormycosis or "black fungus" are the terms used interchangeably. The rapid growth of tissue necrosis presenting as "rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated disease" are various clinical forms of mucormycosis. The patient's prognosis and survival can be improved with proper surgeries using an endoscopic approach for local tissue protection in conjunction with course of appropriate conventional antifungal drug like Amphotericin-B and novel drugs like Rezafungin, encochleated Amphotericin B, Orolofim, and SCY-078 which have been explored in last few years. This review provides an overview of mucormycosis including its epidemiology, pathophysiology, risk factors, its clinical forms, and therapeutic approaches for disease management like antifungal therapy, surgical debridement, and iron chelators. The published patents and ongoing clinical trials related to mucormycosis have also been mentioned in this review.

Keywords Antifungal therapy · Black fungus · COVID-19-associated mucormycosis · Pulmonary mucormycosis · Rhino-orbital-cerebral mucormycosis

Abbreviations

ACE-2	Angiotensin converting enzyme-2
AIDS	Acquired immunodeficiency syndrome
AMB	Amphotericin B
CAM	COVID-19-associated mucormycosis
CKD	Chronic kidney disease
CT	Computed tomography
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
GRP78	Glucose-regulated protein 78 kDa
HSCT	Hematopoietic stem cell transplants
MRI	Magnetic resonance imaging

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PSZ	Posaconazole
ROCM	Rhino-orbital-cerebral mucormycosis
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus-2
SOT	Solid organ transplants

Introduction

Mucormycosis which is known by the term black fungus is a mycotic illness caused by a rising number of zygomatic fungi. It is a fungal disease which gets spread by fungus of Mucorales order and zygomycotic families (Kwon-Chung 2012). The main cause of this infection is exposure to air contaminated with spores which affects the lower and upper part of the respiratory tract leads to sinusitis, pulmonary infection, and rhino-cerebral mucormycosis. This infection rarely spread to cutaneous tissues, central nervous system, and other body organs, but infection can spread to various adjacent organs and is quite prevalent if infected patients will not undergo immediate surgeries and medical treatment. Rhino-orbitocerebral, cutaneous, disseminated, gastrointestinal, and pulmonary mucormycosis are the major clinical forms observed in infected individuals. Immediate treatment is required due to quick progression and tissue destruction characteristics of this infection. The delayed commencement of mucormycosis treatment is related with high death rate (Chamilos et al. 2008a, b). Early diagnosis and adopting a therapeutic approach, as well as prompt participation of an integrative radiological, surgical, medical, and lab-based team is required to maximize survival rates. The mucormycosis is commonly observed in patients having uncontrolled Diabeties mellitus (DM) with ketoacidosis and metabolic acidosis, corticosteroid therapy, bone marrow or organ transplantation, neutropenia, trauma, wounds, cancerous hematological abnormalities, and in hemodialysis patients on deferoxamine therapy (Ibrahim et al. 2012). Immunocompromised individuals having weaker immune systems, such as those who abuse drugs, take insulin for diabetes, undergo cancer treatment, or have AIDS/HIV are more likely to get this infection. Disfiguring surgical debridements and other antifungal therapies cannot save the lives of people infected with mucormycosis; the overall mortality rate is approximately 50% and can arrive at 100% in people with underlying diseases or prolonged neutropenia (Gleissner et al. 2004; Spellberg et al. 2005).

In Wuhan (China), an unusual zoonotic epidemic first emerged in the month of December 2019 and the Coronavirus disease 2019 (COVID-19) started to spread, which is acquired by novel severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), and have tendency to induce variety of symptoms ranging from moderate to high-grade pneumonia. Coronavirus is classified as RNA virus of the coronaviridae subfamily (Khan et al. 2021; Umakanthan et al. 2020). The incubation time of COVID-19 is 1–2 weeks and is transmitted by both symptomatic and asymptomatic infected patients (Hojyo et al. 2020). The clinical signs of COVID-19 infection are Pyrexia, dry cough, chest congestion, muscle weakness, difficulty in breathing, muscle pain, along with other clinical complications. Over 200 million people have been infected and over 4 million died as a result of this virus. The COVID-19 is associated with hypoxia, suppression of immune system, iron loss in the host, hyperglycemia related to diabetes mellitus, and longer hospitalizations. These clinical complications create an ideal environment for opportunistic fungal infections in individuals suffering from COVID-19. The immune system gets activated in response to a fungal infection, which can be the primary cause of illness. The mechanism of infection and the risk of complications vary depending on the type of fungus responsible for the infection. The multi-infected condition may act to enhance the inflammation of systemic components that leads to delayed recovery, resulting in requirement of higher treatment approaches, the need for intensive care, and the danger of mortality. When a virus binds to a target host cell, it produces various cytokines mainly interleukin-6 (IL-6) and activates the nuclear factor kappa B which leads to pro-inflammatory condition marked by a rise in macrophages and cytokines levels. The prevailing cytokines storm and immunological imbalance in COVID-19 may result in failure of the respiratory system, coagulation, failure of body organs, and other clinical complications (Hariharan et al. 2021). The increased level of cytokine reaction can result in T-cell depletion which is common in persistent viral conditions. COVID-19 individuals have less numbers of CD4 + helper T cells (200 cells/L), which enhances vulnerability to fungal infection development. Because CD4 + helper T-cells play an important role in successful immune reaction against invading microbes, and gives signal of immunogenic condition of patients (Diao et al. 2020; Gangneux et al. 2020; Luckheeram et al. 2012; Song et al. 2020). According to International Diabetes Federation, India has an extremely high incidence rate of type 2 diabetes mellitus and it is a well-known risk factor for mucomycosis (Mehta and Pandey 2020a, b). The patients suffering from COVID-19 are identified with additional serious opportunistic infections like gram-negative bacteria, Pneumocystis jiroveci pneumonia (PCP), oropharyngeal candidiasis, *Staphylococcus aureus*, pulmonary aspergillosis, and bloodstream candidiasis (Szarpak et al. 2021). Due to availability of more adequate diagnostic approaches at the turn of the twenty-first century, the mucormycosis has been classified as an emerging invasive fungal infection with high fatality rate of approximately 75–87% (Pagano et al. 2020). The objectives of this comprehensive review are focused on overview of mucormycosis including its pathophysiology

and epidemiology, various predisposing factors, common clinical forms of mucormycosis and various therapeutic approaches. For this purpose, an extensive search of the literature was conducted using the Google Scholar, PubMed, and ScienceDirect databases. Literature review was executed from papers published in peer reviewed journals from the year 2000 to year 2022. The recently published patents and clinical status related to mucormycosis has also been focused in this review.

Pathogenesis and pathophysiology of mucormycosis

The mucormycosis infection is caused by inhalation and entry of mucorales spores into the respiratory tract. These spores can reach inside the nasal cones or in the pulmonary alveolar region. The sequence of events that leads to tissue hyphal growth is mostly unknown. Mucormycosis is characterized by hyphal invasion of blood vessels which is the most prominent characteristic of this infection. Hemorrhage, thrombosis, infarction, and tissue necrosis are all symptoms of this invasion. Mucormycosis and zygomycosis are two terms that are frequently used interchangeably. The latter term refers to diseases caused by fungi belonging to the Zygomycota phylum (which included Entomophthorales and Mucorales). Entomophthorales fungi are uncommon pathogens that cause persistent cutaneous as well as subcutaneous infections which are usually restricted to tropical environments. The organisms *Rhizopus*, *Rhizomucor*, and *Absidia* are most typically isolated from mucormycosis patients. *Mucor*, *Cunninghamella*, *Mortierella*, *Saksenaea*, and *Apophysomyces* were also found in mucormycosis patients, although these were diagnosed in considerably lower numbers (Toumi et al. 2012). The order Mucorales contains 14 families out of which various species of few families has been depicted in Table 1 (Onyango et al. 2002). The *Rhizopus oryzae* is the prevalent causative pathogen recovered from infected mucormycosis individuals, accounting for 70% of all mucormycosis cases (Ibrahim et al. 2012). Mucorales are widespread causative agents that play an important role in starting and promoting the decomposition of organic matter. Because exposure to these fungi spores is unavoidable, the rarity of infection caused by Mucorales is an indicator of their relative avirulence. Infection caused by one of the Mucorales, on the other hand, indicates a serious underlying susceptibility. Mucorales are non-fastidious organisms that can survive at a broad range of climatic conditions (25 to 55 °C) while the ideal temperature for significant Mucorales species is 28–30 °C (Pagano et al. 2020). At a temperature of 37 °C, isolates collected from clinical specimens will also proliferate. These organisms are aerobic which can proliferate after 2–5 days of incubation in the microbiology laboratory. In a single hospital in Spain, *Lichtheimia* spp. was found as the leading cause of mucormycosis, showing geographic diversity and the need to understand local epidemiology (Cornelyet al. 2019; Guinea et al. 2017). *Apophysomyces* spp. was the second most usually isolated agent in Indian investigations (Chakrabarti et al. 2006; Chakrabarti and Singh 2014). *Apophysomyces* and *Saksenaea* spp., which are most prevalent in Asia, are virtually invariably accountable for cutaneous mucormycosis infection in immunocompromised patients (Prakash et al. 2016). *Rhizopus homothallicus*, *Saksenaea erythrospora*, *Thamnostylum lucknowense*, and *Mucor irregularis* are among the new species that have emerged in recent years (Chakrabarti et al. 2010; Lu et al. 2013; Xess et al. 2012).

Patients who have less number of phagocytes or have decreased phagocytic activity are obviously more prone to mucormycosis, according to clinical and experimental findings. Patients who are severely neutropenic are more susceptible to get mucormycosis (Binder et al. 2014). The neutrophils are playing an important role in suppressing fungal spore growth. Furthermore, typical host mononuclear and polymorphonucleated phagocytes destroy Mucorales by production of oxidative metabolites, defensins, and cationic peptides. Ketoacidosis, diabetes, and corticosteroids all affect phagocytes, but the exact mechanisms are unknown (Binder et al. 2014; Spellberg et al. 2005). The mucorales must have distinct virulence features that allow the organism to take advantage of particular condition of immunosuppressive and physiologic impairment that incline individuals to mucormycosis. One such attribute is capacity to get iron from infectious host. Iron is a necessary element since this

Table 1 Representation of various families of pathogenic mucorales and their species

Family	Species
Mucoraceae	*Rhizopus oryzae*, *R. rhizopodiformis*, *R. rhizopodiformis*, *R. microspores*, *Absidia corymbifera*, *Mucor cirrcinelloides*, *M. pusillus*, *M. miehei*, *Rhizopus homothallicus*, *Mucor irregularis*
Mortierellaceae	*Mortierella wolfii*
Cunninghamellaceae	*Cunninghamella elegans*, *C. bertholletiae*
Saksenaeaceae	*Saksenaea vasiformis*, *Saksenaea erythrospora*
Syncephalastraceae	*Syncephalastrum* sp.

participates in many key cellular activities for growth and development of cell. The pathogenic viruses adopt numerous ways to extract iron from their hosts. The recent research has shown that persons with ketoacidosis who are susceptible to mucormycosis depend critically on amount of available free iron in their plasma. The iron is bounded to carrier proteins of host like ferritin, lactoferrin, and transferrin in mammals. This sequestration process prevents the harmful effects of free iron (Ibrahim et al. 2012; Ibrahim 2014; Tabassum et al. 2021). Mucormycosis infections are distinguished by widespread angioinvasion, which results in thrombosis of vascular compartment and subsequently leads to tissue necrosis (Ibrahim et al. 2012; Mehta and Pandey 2020a, b; Tabassum et al. 2021). The ischemic necrosis of damaged tissue can hinder white blood cells and antifungal drugs from reaching infection sites. This angioinvasion most likely adds the ability of organisms to hematogenously spread to additional target organs of body. Consequently, dissemination through endothelium lining of the blood arteries is thought to be significant phase in *R. oryzae*'s pathogenetic approach. Determining the mechanisms behind these pathogenic processes may result to novel techniques for preventing and/or treating mucormycosis (Ben-Ami et al. 2009; Chayakulkeeree et al. 2006; Spellberg et al. 2005). Figure 1 describes various steps involved in pathogenesis and pathophysiology involved during progression of Mucormycosis. Mucormycosis gets spread by inhaling, ingesting, or directly inoculating Mucorales spores into punctured skin. Because of epithelial cell injury in a susceptible host, these spores infiltrate tissues by attaching to exposed extracellular matrix (ECM) proteins. Mucorales infiltrate epithelial cells and secreted proteases to enter into ECM protein. Mucorales avoid tissue macrophage mediated death and infiltrate blood arteries by attaching to ECM proteins and invades endothelial cells. Mucorales proliferate in an infiltrated blood vessel in affected host in presence of free iron (e.g., iron release from transferrin (T) through a proton-mediated process in DKA individuals) and due to inefficient polymorphonuclear leukocytes. Mucorales penetrate endothelial cells by adhering to GRP78, which is highly expressed and relocalized to cell surface endothelium in DKA individuals with elevated glucose and iron levels and finally, fungal hyphae enter the blood vessels.

Epidemiology of mucormycosis

The inhalation of fungal spores which are present in atmospheric air or direct injection of any pathogenic agents in mucus membrane or damaged skin can cause the majority of human illnesses. Mucorales are thermo-tolerant and prefer to live in decomposing organic materials (Petrikkos et al. 2012). Cases of mucormycosis have been reported from all over the globe.

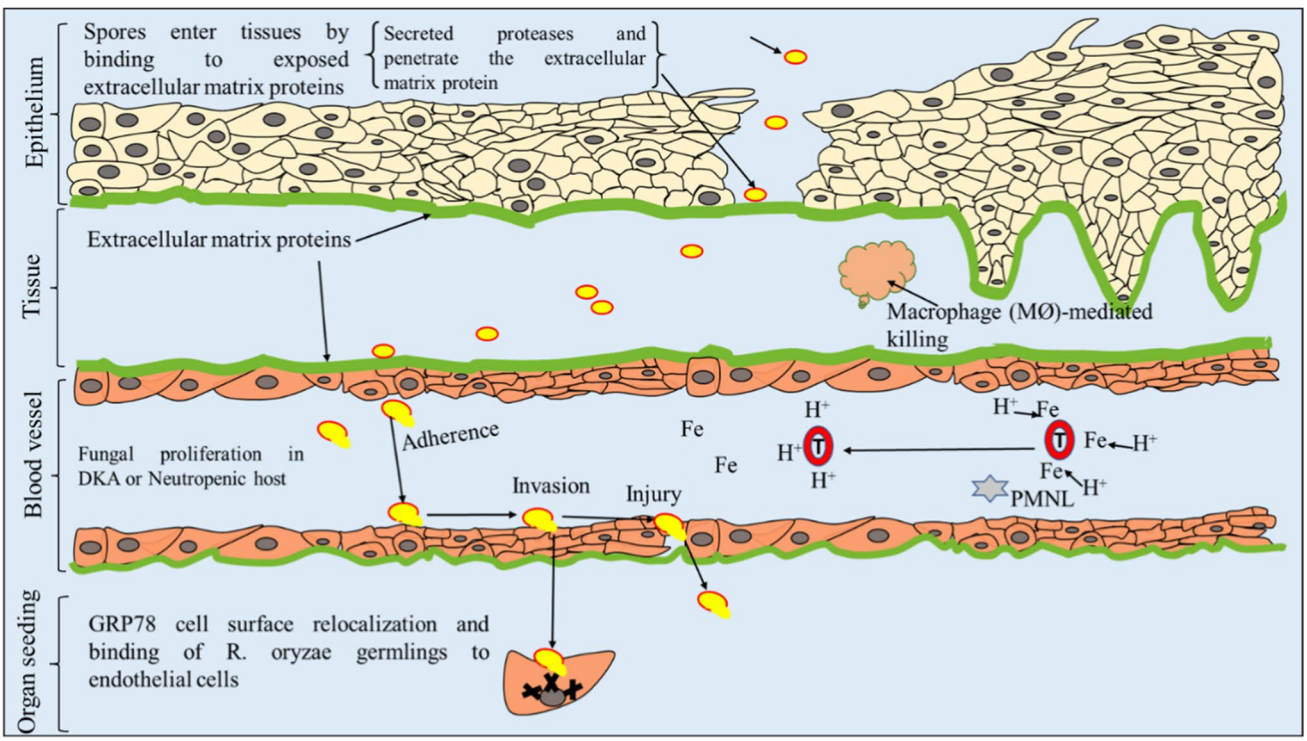

Fig. 1 Schematic depiction of pathogenesis and pathophysiology involved during Mucormycosis progression. PMNL, polymorphonuclear leukocytes; DKA, diabetic ketoacidosis; Fe, iron; T, transferrin; GRP-78, Glucose Regulated Protein-78

There appear to be differences in mucormycosis epidemiology between industrialized and poor countries. Transplantation of hematopoietic stem cells and hematologic malignancies are some of the predominant underlying conditions of mucormycosis infection in well-developed countries. The uncontrollable diabetes mellitus and injuries are well known risk factors to get this infection in underdeveloped countries, particularly in India (Challa 2019; Petrikkos et al. 2012; Prabhu and Patel 2004; Skiada et al. 2011). Due to challenges in clinical diagnosis, exact information on incidence of mucormycosis is limited. On the other hand, as per recent global autopsy data, the most prevalent cause of invasive mycotic illness is mucormycosis, after Candidiasis and Aspergillosis, with the increased number of cases observed in adults and children who are less than one year in age (Dignani 2014). In accord to published research, mucormycosis is 5–10 times less prevalent than the other mycotic infections such as aspergillosis (Chamilos et al. 2006a, b; Kontoyiannis et al. 2005). Nonetheless, mucormycosis is a rare illness, even in individuals who are more prone to get an infection, accounting for 8.3–13% of maximum mycotic infections discovered at autopsy in these individuals (Kume et al. 2003; Suzuki et al. 2013). According to postmortem prevalence analysis, mucormycosis is 10–50 times rarer than candidiasis or aspergillosis with 1–5 instances per 10,000 autopsies (Petrikkos et al. 2012; Suzuki et al. 2013). In addition, diabetes mellitus is a significant underlying condition for mucormycosis in India, but there is a difference in the number of cases in different regions of India i.e., 67% in the north and 22% in the south (Prakash et al. 2019; Sharma et al. 2021). In COVID-19 individuals, the factual occurrence of rhino-orbital mucormycosis is unknown. However, there are many reports of mucormycosis infection in COVID-19, most of which are from India, particularly in diabetic patients who have undergone COVID-19 treatment and recovered, where corticosteroids are administered inadvertently to control severity, resulting in a higher fatality rate and complicating the pandemic (Gupta and Singh 2021; Singh et al. 2021a, b). Mucormycosis has been found in 1–5 instances per 10 thousand autopsies in autopsy studies, leading the illness 10–50 times less prevalent than persistent Candidiasis or Aspergillosis infections (Suzuki et al. 2013; Tietz et al. 1998; Yamazaki et al. 1999). The occurrence of mucormycosis infection is quite high as 2–3% in individuals who are at higher risk, especially those who have undergone transplantation of bone marrow (Maertens et al. 1999).

Risk factors causing mucormycosis

Mucormycosis, often called as black fungus infection, is a new opportunistic infection having an estimated prevalence of 0.005–1.7 per million people (Siddiqui et al. 2006). Nevertheless, the occurrence of mucormycosis infection in India is quite close to 0.14 cases for every 1000 individuals that are about 80 times more than the incidence in well-established nations (Chander et al. 2017). In India, the rise in COVID-19 incidence is associated to rise in reports of extensive mucormycosis infection post-COVID-19, and this trend is expected to continue. While numerous therapy options for COVID-19 have been investigated, glucocorticoids have been proven to enhance survival but can also result in secondary fungal infections. The SARS-CoV-2, corticosteroid usage, and uncontrollable diabetes, these predisposing factors are responsible to rise in the number of invasive mucormycosis infection (Amin et al. 2021). The triggering factors of mucormycosis are mentioned below in Fig. 2.

Diabetes mellitus

DM has been proved to be a main underlying condition among 36–88% of total number of mucormycosis incidences (Roden et al. 2005). Individuals with high sugar levels, especially patients with ketoacidosis, are more prone to get the mucormycosis infection. The mucormycosis infection is mostly observed in patients having uncontrolled DM, but this is uncommon in patients with controlled diabetes. Mucormycosis infection has been linked to type-1 DM, type-2 DM, and also with the secondary DM (Bhansali et al. 2004; Chamilos et al. 2006a, b; Kontoyiannis 2007). DM is a major predisposing factor for intense COVID-19 infection and is also linked with high death rate due to COVID-19 (Wu and Mc Googan 2020). DM alters the innate immunity by altering the function of phagocytes that improves considerably after controlling sugar level (Shodja et al. 2017). Furthermore, affected dendritic cells respond and postpone the stimulation of adaptive immunity. On the other hand, COVID-19 can cause arrival of DM and also DKA which is observed in the recently diagnosed diabetic patients subsequent to COVID-19 infection (Heaney et al. 2020; Hodgson et al. 2015). The ACE-2 is mostly present in lungs, as well as in pancreas which act as COVID-19 doorway receptor. The ACE-2 proteins promote the SARS-CoV-2 entry into the pancreatic islets and may harm beta cells. Furthermore, intense COVID-19 causes resistance to insulin by increasing the release of most of stress hormone like hydrocortisone and various cytokines. Furthermore, uncontrolled DM is a common predisposing factor for mucormycosis, equally in COVID-19 and non-COVID-19 individuals. Mucormycosis is more common in DKA patients. On the human endothelial cells, expression of glucose-regulated protein 78 kDa (GRP78) increases in hyperglycemia which is a critical binding receptor for many mucorales vascular invasion via the spores coat protein (CotH) (Gebremariam et al. 2014; Liu et al. 2010). Also, Rhizopus is involved with the GRP78 on epithelial cells of nasal mucosa, mostly through CotH3 protein in order to attack and disrupt the cells. High levels

Fig. 2 Classification of risk factors causing mucormycosis

of glucose, iron, and ketones (the hallmarks of DKA) drastically increase the proteins expression namely GRP78 and CotH3 that potentially causing ROCM (Alqarihi et al. 2020; Muthu et al. 2021).

Use of corticosteroids

The use of corticosteroids is also one major underlying condition for COVID-19-associated mucormycosis (CAM). On innate and adaptive immune systems, they are acting as powerful immunosuppressant and are producing an extensive range of effects. The corticosteroid-induced hyperglycemia increases the susceptibility to mucormycosis infection since elevated hyperglycemia affects neutrophil and phagocyte activities i.e. impair the ability of phagocytes to eliminate fungal spores (Fuji et al. 2017; Hoang et al. 2020). Dexamethasone had completely inhibited the Aspergillus and Rhizopus phagocytosis in a Drosophila melanogaster model (Chamilos et al. 2008a, b). Dexamethasone and various other steroidal drugs are mostly considered to treat COVID-19 infection; however, their role in progress of COVID-19-associated mucormycosis (CAM) appears undisputed (Patel et al. 2021). The corticosteroids are familiar to increase threat of invasive infections like mucormycosis and aspergillosis. Persistent usage of steroids with a dose of 0.3 mg/kg of steroids for about 21 days in the earlier two months and that has been identified as a determinant of invasive fungal diseases (Donnelly et al. 2020). Recently, a research study found that the doses and durations higher than the current COVID-19 recommendation (Dexamethasone 6 mg for up to 10 days) were linked with an increased incidence of CAM (Patel et al. 2021). More research is needed to determine whether even lower doses are harmful or whether other unknown factors contribute to CAM.

Iron overload

Hyperferritinemia is a defining feature of COVID-19 and it is linked to a higher risk of mortality. Remarkably, ferritin-associated iron causes imperfection in both the adaptive (T-lymphocytes) and innate (neutrophils) immunity in mouse models (Deng et al. 2021; Edeas et al. 2020; Kuvibidila and Warrier 2004). This has been found in an in vitro model that deficiency of iron can cause apoptosis in *R. arrhizus.* Therefore, it is necessary for mucorales to obtain free iron from patients in order to acquire their development and maturation. (Ibrahim 2014; Shirazi et al. 2015). Deferasirox is an iron chelator which prevents the mice from

mucormycosis infection by deprivation of iron but it is not useful in patients. Individuals with excess iron are highly susceptible to develop mucormycosis infection, particularly patients taking iron chelator namely deferoxamine (Ibrahim et al. 2007; Soman et al. 2012; Spellberg et al. 2012). In patients with DKA, acidosis causes a partial dissociation of iron that is bonded to transferrin. The ability of transferrin to chelate iron is eventually impacted by the ketoacid b-hydroxybutyrate. The high level of iron may allow *R. arrhizus* to grow. Deferoxamine therapy chelates the iron and is used to treat iron and/or aluminum overloads in individuals undergoing dialysis, and has been linked to angioinvasive mucormycosis infection. Iron overload, whether from dyserythropoiesis or transfusion, is also a main underlying condition for mucormycosis infection (Vigouroux et al. 2005). Disseminated mucormycosis is the common clinical type of mucormycosis in those patients who are taking Deferoxamine (44%), and this clinical form is linked with elevated mortality rate reaching upto 80% (Torres-Narbona et al. 2007). Nowadays, the Deferoxamine is not used due to emergence of novel iron chelators such as deferasirox and deferiprone, due to which individuals are not getting more susceptible to mucormycosis infection.

Hematological malignancies and transplantation of hematopoietic stem cell

In the USA and Europe, one of the most common diseases for mucormycosis infection was hematological malignancy which ranged from 38 to 62%. Mucormycosis is more common in individuals who suffer from acute myeloid leukemia, undergone transplantation of hematopoietic stem cells, having myelodysplastic syndrome and acute lymphoblastic leukemia during the stage of neutropenia (Pagano et al. 2004; Roden et al. 2005). According to the findings of a multicenter cohort research that was conducted in France, 0.4% of patients of allogeneic hematopoietic stem cell transplantation (HSCT) were found to have mucormycosis (Xhaard et al. 2012). In Italy, one cohort study of patients undergone HSCT found 0.1% cases of mucormycosis between 1999 and 2003 (Pagano et al. 2007). The TRANSNET research on HSCT patients in the USA found that mucormycosis attributed for 8% of invasive mycotic infections with a yearly collective occurrence of 0.29% (Kontoyiannis et al. 2010; Park et al. 2011). The occurrence of mucormycosis in individuals undergoing allogeneic stem cell transplantation or autologous is less than that observed in individuals with myeloid leukemia, that ranges from 0.9 to 2.0%, with the maximum proportion experienced by individuals with the graft-versus-host disease (Baddley et al. 2001; Neofytos et al. 2009; Petrikkos et al. 2012).

Solid organ malignancies and transplantation

The malignancies of solid organ and recipients of solid organ transplants (SOT) are also key underlying conditions for mucormycosis infection, even though only in a small percentage of incidence. Mucormycosis accounts a less percentage of invasive mycotic infections in case of SOT individuals. Furthermore, it is related to a high mortality rate. Depending on SOT type, the prevalence rate ranges from 0.4 to 16.0%, 0.2 to 1.2% in kidney transplant patients, 0 to 1.6% in patients who have undergone a liver transplant, 0 to 0.6% in heart transplant patients, and 0 to 1.5% in lung transplant patients (Bitar et al. 2009; Petrikkos et al. 2012; Roden et al. 2005). Moreover, mucormycosis infection spread to other organs frequently after graft rejection and treatment. Individuals with kidney failure (58%), DM (38%), and earlier antifungal treatment of caspofungin or voriconazole (26%) are highly susceptible to get mucormycosis (Singh et al. 2009).

Long-term use of voriconazole

In many research centres, the development and broad use of anti-Aspergillus agents, particularly voriconazole, in people with hematological malignancies and recipients of hematopoietic stem cell transplants increase the mucormycosis cases (Kontoyiannis et al. 2005; Trifilio et al. 2007). The prospective randomized studies comparing voriconazole prophylaxes with itraconazole or fluconazole prophylaxes in allogeneic transplant patients did not prove this finding (Antinori et al. 2009). Because the patients in both studies had a low risk of invasive fungal infections and mucormycosis infection, the utility of voriconazole is still controversial. Despite the ambiguity around this risk, clinical professionals must be aware that mucormycosis infection can develop in high-risk patients receiving voriconazole. Mucormycosis developed after voriconazole treatment of persistent aspergillosis in individuals with blood cancer has a high mortality rate. The awareness of this entity for clinical professionals is critical in patient management. It is vital to have strong index of suspicion for mucormycosis for proper diagnosis and accurate laboratory diagnostic approaches using molecular and conventional techniques are the needful methods for managing this catastrophic infection (Sharifpour et al. 2018).

Dysfunction of endothelial cells

COVID-19 is linked with dysfunction of endothelium. In individuals with intense COVID-19, autopsy studies revealed rigorous injury of endothelial cells and is associated with the existence of intracellular virus as well as disruption of cell membranes (Meini et al. 2020). Another explanation for the rise in mucormycosis cases is the damage of endothelium and endothelialitis observed in

severe COVID-19 patients. ACE-2 receptors are present in endothelial cells of the lungs and endothelialitis could be an immune reaction in response to direct viral infection. In COVID-19 individuals, autopsy reports revealed the existence of severe injury of endothelium with interrupted cellular membrane, microangiopathy, extensive thrombosis, and angiogenesis in the pulmonary vasculature (Meini et al. 2020). Adherence to endothelium, as well as penetration, is crucially important in initial stages of mucormycosis infection. The vascular endothelitis also provides an easy path for Mucorales to enter inside the bloodstream which leads to increase the risk of complications (Rudrabhatla et al. 2021).

Human immunodeficiency virus or AIDS

Mucormycosis is extremely uncommon in individuals having human immunodeficiency virus (HIV) or AIDS. Only two patients with mucormycosis were found in an extensive research examination of 1630 autopsies that died of AIDS (Antinori et al. 2009). This low occurrence shows the rarity of mucormycosis infection in HIV-infected individuals in comparison to other immunocompromised patients. The majority of mucormycosis incidences in HIV-infected individuals are linked to the use of intravenous drugs (Roden et al. 2005; Skiada et al. 2011). In 2016, approximately 67 cases of mucormycosis infection were reviewed among HIV patients and found that intravenous drug use was the predominant risk factor, followed by 29.7% neutropenia, 15% steroid usage, and 10% diabetes mellitus as the other underlying diseases (Moreira et al. 2016).

Environmental factors

The fungi that cause mucormycosis infection and its spores are found in decomposed matter and soil that belongs to order mucorales. The organism reproduces quickly in favorable conditions and the percentage of spores in the air increases. In spite of the fungal prevalence, mucormycosis infection is most commonly seen as an opportunistic illness in immunocompromised patients. In hospitals, outbreaks of mucorales cutaneous infection have been linked with contaminated sticky tape bandages, cloths, and tongue depressors made up of wood (Ribes et al. 2000; Spellberg 2017; Walther et al. 2020). Pulmonary and rhino-orbital mucormycosis infection has been seen less frequently upon contact contaminated air (from dirty air conditioners, ongoing building constructions, or ventilating systems) (Walther et al. 2020). In an Indian study, approximately 9% of the mucormycosis infection (largely cutaneous) incidents were nosocomial (Chakrabarti et al. 2009).

Miscellaneous factors

Repurposing of some biological drugs for the treatment of COVID-19 infection, like interleukin-1 and interleukin-6 inhibitors, Janus kinase inhibitors, tumor necrosis factor may raise the susceptibility for infections (Cavalli et al. 2020). Several unproven COVID-19 therapies were widely used around the world, especially in India (Beović et al. 2020). The impact of antibiotic overuse on various superadded infections is well documented. *Staphylococcus epidermidis* as well as *Staphylococcus aureus* both are frequent nasal flora constituents and were shown to prevent the development of common saprophytic fungi *Rhizopus arrhizus* (Singh and Kumari 2021). The improper use of antifungal and antibacterial drugs may disrupt the fine balance of the nasopharyngeal and respiratory epithelial mycobiome and microbiome (Muthu et al. 2021). Mucormycosis infection is not only observed in immunocompromised patients, significant incidences are observed in immunocompetent individuals as well with no known underlying predisposing conditions. Two meta-analyses from different time periods found that 19% cases of mucormycosis infection happen in immunocompetent patients also (Jeong et al. 2019; Wu and Mc Googan 2020). These patients frequently develop cutaneous mucormycosis as a result of burns, surgery, trauma, contaminated dressings, or injections (Cavalli et al. 2020; Chakrabarti et al. 2006).

Clinical forms of mucormycosis

Mucormycosis infection is an invasive mycotic illness associated with COVID-19 with an increased mortality rate acquired by widespread fungi having hyphae which belongs to the Mucorales order. Due to an increase in the population at risk and improving diagnostic techniques, the reported incidence of mucormycosis has risen over time (Bitar et al. 2009). This fungal disease is distinguished by widespread necrotizing vasculitis, which leads to thrombosis and subsequent tissue destruction. The primary site of mucormycosis infection differs depending on the order of Mucorales or the predisposing conditions of susceptible hosts (Jeong et al. 2019; Wu and Mc Googan 2020). The common clinical forms of mucormycosis are mentioned below in Fig. 3.

Rhino-orbito-cerebral mucormycosis (ROCM)

ROCM is inevitably a deadly mycotic disease which primarily influences the immunocompromised individuals. There is insufficient data from India on the outcomes of individuals with ROCM (Singh et al. 2021a, b). It is one of the prevalent clinical forms of mucormycosis. This is acquired by inhalation of spores which permits the mold to expand in

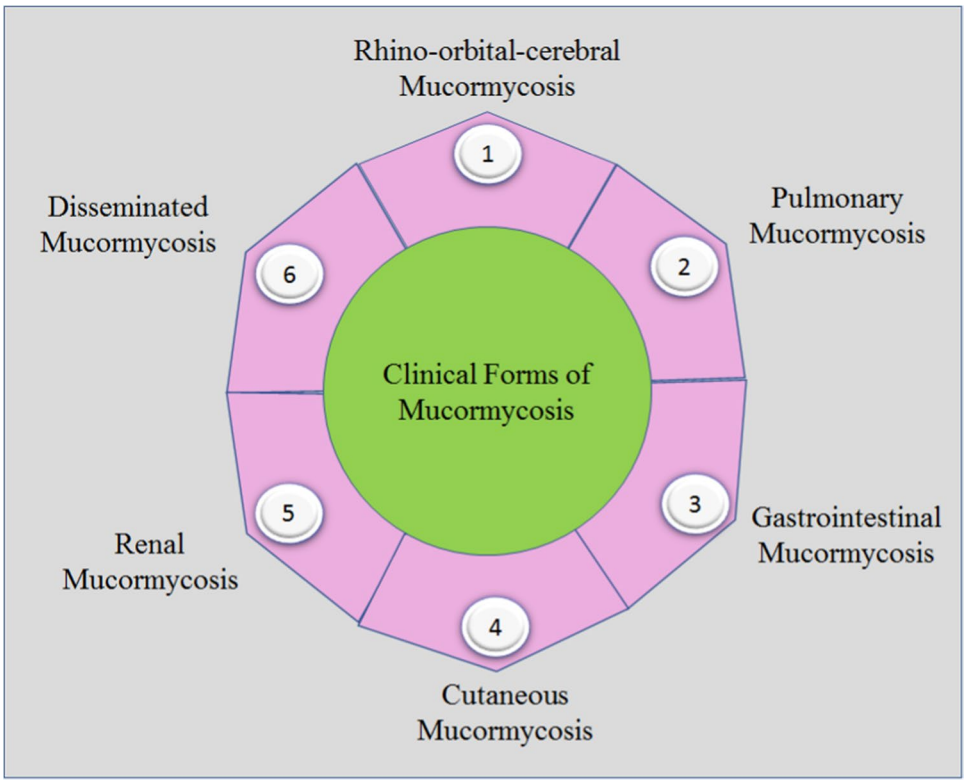

Fig. 3 Various types of common clinical forms of mucormycosis

adjoining nasal cavities. This disease can spread quickly to adjoining tissues, including the sphenoid sinuses, palate, orbits, and cavernous sinuses, subsequently spread to various cerebral regions. The destruction of these infected tissues was reported as black necrotic tissue and is a concerning indication of local extension. DM is the commonest predisposing risk factor in a meta-analysis of 175 ROCM incidences which was later published between 1994 and 2005 and contributed to 64% cases of ROCM, followed by hematological malignancy and kidney diseases which produced 15% and 13% cases of ROCM, respectively (Vaughan et al. 2018). ROCM remains the main popular type of infectious ailment, contributing for one-third to one-half of all incidences of mucormycosis. Approximately 70% of rhino-cerebral incidence which is also known as craniofacial has been observed in diabetic individuals having ketoacidosis (Spellberg et al. 2005).

ROCM has also been reported in individuals who have undergone SOT or have chronic neutropenia (Gleissner et al. 2004; Petrikkos et al. 2003). The early symptoms of ROCM infection are similar to periorbital cellulitis or sinusitis including eye or face pain and lack of sensation in facial area and subsequent conjunctival suffusion, soft tissue swelling and blurred vision (Dhiwakar et al. 2003; Talmi et al. 2002). Fever is quite uneven which may be absent in up to 50% of the patients. Leukocyte count usually remains high as the host has functional bone marrow (Spellberg et al. 2005). Even though the nasal and paranasal sinuses are primary locations of mold inoculation, these combative fungi propagate and extend to orbital and various parts of central nervous system through haematogenous route or direct extension, resulting in development of life-threatening ROCM. Infection of SARS-CoV-2 causes immunosuppression by disturbing the T-lymphocytes, resulting in lymphopenia, which plays a critical role in cell-mediated immunogenicity and altering the ratio of neutrophils and lymphocytes (Gangneux et al. 2020; Song et al. 2020). The existence of comorbid illness such as DM with simultaneous corticosteroid and other immunomodulating agent therapy for treatment of normal to severe cases suppresses the immune system of patients and leads to aggressive mycotic infections throughout the duration of the disease (Garg et al. 2021; Mehta and Pandey 2020a, b).

Pulmonary mucormycosis

Another common site for mucormycosis infection is involvement of the pulmonary tract, which is frequently seen in organ transplant recipients and patients having hematological disorders (Jeong et al. 2019; Prakash et al. 2019). The foremost underlying condition for pulmonary mucormycosis has been hematological malignancy while other causal conditions includes transplant of hematopoietic stem cells, diabetes, transplant of solid organs, and renal diseases (Feng and Sun 2018; Prakash and Chakrabarti 2019). The high fever, chest pain, persistent cough, dyspnoea, and hemoptysis

are the common symptoms of pulmonary mucormycosis. The diagnosis of pulmonary mucormycosis infection is still challenging. Pulmonary mucormycosis is generally unilateral, but it can be bilateral, hilar, or mediastinal. Upper lobe involvement is common in unilateral lung disease, followed by involvement of lower and middle lobes. Involvement of multi-lobes is observed in about half of all pulmonary mucormycosis scenarios (Feng and Sun 2018). Diagnostic imaging studies of pulmonary mucormycosis patients have indicated the presence of pulmonary infiltrates and consolidation, pleural effusion, thickly walled cavities, multiple nodules, pneumothorax, mediastinal lymphadenopathy, and air crescent. The therapies of pulmonary mucormycosis include combination of antifungal and surgical treatment. Pulmonary mucormycosis has a higher mortality rate than other localized types of mucormycosis infections (Prakash and Chakrabarti 2019; Spellberg et al. 2005).

Cutaneous mucormycosis

Cutaneous intervention in mucormycosis infection occurs as a result of either direct fungus inoculation by traumatic injuries known as primary mucormycosis or dissemination by blood-borne infectivity or spreaded contiguously called as secondary mucormycosis (Vinay et al. 2014). In general, there are two types of primary cutaneous mucormycosis which includes rapidly developing angioinvasive necrotising type or slowly chronic granulomatous type. The penetrating trauma is the most common cause of cutaneous mucormycosis while other predisposing factors includes intramuscular injection in substandard healthcare premises, car accidents, surgery, open wound trauma, contaminated dressings, natural disasters, burns, animal bites, and scratches (Wu and Mc Googan 2020). The most common symptoms of cutaneous mucormycosis are necrosis, purulent discharge, redness, swelling, and mouldy appearance. The localized infection is observed in 32–56% of hosts and is typically limited to subcutaneous and cutaneous tissue without intruding into adjoining sites. The deeper extension includes involvement of muscles, tendons, and bones that is generally observed in 24–52% of patients. In these patients, erythematous necrotic eschar with necrotizing fasciitis appears as common manifestation of infection. Cutaneous mucormycosis is a type of disseminated infection that involves other non-contiguous sites apart from the cutaneous sites and is observed in 16 to 20% of cutaneous infections (Feng and Sun 2018; Wu and Mc Googan 2020). The treatment for cutaneous mucormycosis includes the combination of systemic antifungal agents and surgical procedures (Lelievre et al. 2014). European conference on infections in leukemia-6 recommends surgery in conjunction with Amphotericin-B for all grades of soft tissue disease (Tissot et al. 2017).

Gastrointestinal mucormycosis

The least common type of mucormycosis is primary gastrointestinal disease. It can spread by eating unhygienic food, such as dried bread products and fermented milk, but it can also be acquired through healthcare-associated contact with dirty surgical devices. The most prevalent site of infection has been presented as the stomach, and thereafter the colon, small intestine, and also esophagus (Serris et al. 2019). In a research study of 31 cases, the main prevalent type was intestinal disease followed by gastric disease (Dioverti et al. 2015). Hematologic malignancy and SOT are the two the most prevalent causes. The premature neonates have also been reported to have gastrointestinal mucormycosis (Rammaert et al. 2012). Peritoneal dialysis and DM are the most common underlying conditions in adults; however, malnutrition and prolonged use of antibiotics are associated extensively with children. The most complicated form of the disease to diagnose ante-mortem is gastrointestinal mucormycosis, which is frequently observed in underweight babies, malnourished individuals, and peritoneal dialysis patients (Kaur et al. 2018; Wu and Mc Googan 2020). Individuals with hematological malignancy, neutropenia, and solid organ transplants are majority of immunocompromised individuals with gastrointestinal mucormycosis infection (Kaur et al. 2018). Emergency surgery along with intravenous Amphotericin B is the most recommended treatment strategy for gastrointestinal mucormycosis. Since GI symptoms are quite non-specific, therefore diagnosis is frequently deferred or missed due to which the mortality rate remains high at 57% (Dioverti et al. 2015).

Disseminated mucormycosis

The mucormycosis infection can spread from one to other body organs hematogenously (Liu et al. 2000; Tomita et al. 2005). The lungs are usually associated with dissemination process; however, this can also occur through extensive cutaneous lesions, gastrointestinal tract, and burns. Although the cenral nervous system is a common location of spread, lesions in the liver, heart, spleen, and other organs can also be causative reasons identified in patients (Petrikkos et al. 2012). Individuals with high iron intake, particularly those on Deferoxamine therapy, significant suppression of immune system, e.g., patients who have undergone transplants of allogeneic stem cell with graft-versus-host disease, the patients on steroid therapy, intense neutropenia, and active leukemia, are typical risk individuals for the disseminated type of mucormycosis (Gonzalez et al. 2002; Petrikkos et al. 2012; Prabhu and Patel 2004). The systemic staging with cerebral MRI and a sinus thoracoabdominal CT scan must be executed to diagnose disseminated mucormycosis. The patients infected with disseminated mucormycosis had the

maximum death rate (58–79%) in comparison to other clinical presentations of mucormycosis (Lanternier et al. 2012; Skiada et al. 2011).

Renal mucormycosis

Several Indian studies found that the patients of isolated renal mucormycosis infection increased from 5.4 to 14% of entire incidences of mucormycosis (Chakrabarti et al. 2006; Prakash et al. 2019). There was no underlying disease in approximately 33–100% of renal mucormycosis infection cases in China and India (Ambrosioni et al. 2010; Prakash et al. 2019). Early detection of renal mucormycosis can be aided by computer tomography and ultrasound scans. A CT scan of abdominal part reveals bilaterally inflamed kidneys, bulging of the renal pelvis, and infarction of parenchyma (Bhadauria et al. 2018). In India, renal mucormycosis infection in patients having the normal immune system is another clinical entity. The analysis of several mucormycosis case series from India illustrated that 33–100% of renal mucormycosis infection were observed in immunocompetent patients (Gebremariam et al. 2015). Hemodialysis and CKD were considered critical risk determinants in patients with renal mucormycosis (Prakash et al. 2019). Renal mucormycosis can affect the kidneys unilaterally or bilaterally. The fever, haematuria, flank pain, severe kidney injury, flaky white crystals in the urine, and acute kidney injury are common symptoms reported in patients (Bhadauria et al. 2018).

Approaches for treatment of mucormycosis

Mucormycosis can be effectively managed if various sectors work together in collaborative and interdisciplinary manner. Because of the high mortality rate, even the smallest clinical suspicion would prompt the start of antifungal treatment. Surgical debridements, as well as antifungal medicines, are used to treat this condition. Roden et al. discovered that antifungal therapy and combined surgery was highly related to higher survival rates (69%) in a multivariate investigation of 929 recorded cases of mucormycosis, whereas fatality was virtually definite (97%) for individuals who received no treatments (Sipsas et al. 2018).

Antifungal therapy

Amphotericin B (AMB) is the primary treatment for this disease, and it has a significant impact on patient outcomes. This was demonstrated in a research study of 70 individuals having mucormycosis who did not receive AMB therapy on time (starting therapy 6 days following diagnosis), which resulted in an almost doubling in mortality 12 weeks after diagnosis (Chamilos et al. 2008a, b). AMB therapy is needed until clinical recovery is shown, which generally involves a couple of weeks. Compared to AMB, deoxycholate, a less expensive and more toxic alternative, intravenous AMB lipid formulation is commonly used (Honavar 2021). Metabolite repletion should also be monitored after Amphotericin therapy. Regular intravenous saline hydration and electrolyte replenishment were found to reduce metabolic irregularities and renal problems related with AMB poisoning in a clinical cohort trial of 368 individuals (Bicanic et al. 2015). AMB has been found ineffective against *Apophysomyces* and *Cunninghamella* isolates (Alastruey-Izquierdo et al. 2009). Because of its nephrotoxic properties, patients with compromised kidney function must be put on triazoles, such as Isavuconazole and Posaconazole (PSZ), which suppress ergosterol production in the cell membrane of fungal cells. In individuals who could tolerate AMB, these can also be administered as rescue treatment and as a step-down therapy (Hof 2006). Despite the fact that antifungal combination treatment is not currently recommended in any of the major clinical guidelines, more trials are required to determine its efficacy (Sipsas et al. 2018). Isavuconazole, a drug for mucormycosis that was newly approved in the Europe and U.S., has the possibility to become the standard treatment for fungal infections. The absence of cyclodextrins group which cause nephrotoxicity is a considerable advantage of Isavuconazole as compared to voriconazole. A once-daily regimen is also possible due to its long half-life (Spellberg and Ibrahim 2010). According to multicentric clinical trials, individuals receiving Isavuconazole or Amphotericin B have same mortality rate. In DKA mice infected by Rhizopus spp., combined therapy of Amphotericin B Lipid Complex and caspofungin was found to have a considerably higher survival rate than placebo or monotherapy. Liposomal Amphotericin-B along with anidulafungin or micafungin has shown improved results in disseminated mucormycosis. In the present circumstances, lipid formulations of Amphotericin B (LFAB)-echinocandin therapy for mucormycosis must be given at levels permitted by USFDA (Falci and Pasqualotto 2013). Rezafungin, encochleated Amphotericin B, orolofim, and SCY-078 are some of the new antifungal drugs currently being tested (Brunet and Rammaert 2020; Van Daele et al. 2019). Olorofim belongs to the orotomides, a novel antifungal agent that block the activity of dihydroorotate dehydrogenase (DHODH), an important enzyme for pyrimidine synthesis. A new glucan synthase inhibitor SCY-078 is ineffective against Mucorales (Lamoth and Alexander 2015). It also has low antimicrobial activity against Mucorales (Jørgensen et al. 2018). Antifungal drugs that are effective against saprophytic fungi are currently developed. VT-1161 is a new blocker of CYP-51 which is a fungal enzyme with mucorales activity in vitro. In *R. arrhizus* models, VT-1161 used as a curative or prophylactic therapy increased the survival of mice with neutropenic

(Gebremariam et al. 2015, 2017). In a murine model, SCH 42427, a broadly acting triazole, was proven to be effective (Sugar and Liu 2000). APX001A (previously E1210) is an antifungal drug which blocks the Gwt1 protein. Gwt1 is a "glycosylphosphotidyl inositol post-translational modification pathway" surface protein. Despite the fact minimal inhibitory concentrations for mucorales are quite high, several researchers have demonstrated that APX001A is as efficacious as AMB in protecting mice in a *R. delamar* model (Miyazak et al. 2011; Rivero-Menendez et al. 2019; Sipsas et al. 2018). Finally, PC1244, a novel prolong acting antifungal azole, has been proven to have antifungal action against Mucorales with MICs ranging from 0.25 to 2 mg/L (Colley et al. 2018), and yet it has not been evaluated in vivo. Colistin has shown moderate in vivo and in vitro action against Mucorales among antibiotics (Ben-Ami et al. 2010).

Adjunctive therapies

In individuals having blood-related problems, any attempt to reverse neutropenia must be attempted, either employing hematopoietic growth agents or, in some cases, infusions of white blood cells. Persons suffering from corticosteroid-induced immunosuppression, like those suffering from immunological diseases must be weaned or shifted to non-steroidal medication if possible. Individuals having HIV/AIDS must start taking antiretroviral therapy to strengthen their immune system. Sugar control is crucial for people who have uncontrolled diabetes and/or ketoacidosis. Iron chelator therapies are still a possible treatment option for individuals with DKA. Individuals with diabetes particularly those having ketoacidosis could benefit from chelating with unbound iron. Physicians should also emphasize the treatment of any additional comorbidities that may exist (Alekseyev et al. 2021).

Hyperbaric oxygen treatment has been demonstrated to be an adjuvant therapy when used in combination with other therapies. Increased oxygen pressure is suggested to stimulate the neutrophil function and enhance AMB activity by lowering acidosis. Finally, raising oxygen pressure promotes wound healing and reduces fungal development through inhibition of spore germination. Consequently, hyperbaric oxygen therapy (HBOT) for mucormycosis is generally suggested as an adjunct to surgical and antifungal treatment (Sipsas et al. 2018). In such situations, healthcare practitioners can play an important role to enhance the clinical result. Because of the difficulty in diagnosing these diseases, the late initiation of antifungal therapy can be linked with a significant incidence of deaths. At present, the most prevalent form of diagnosis is blood culture. Due to their poor sensitivity, cultures need a considerable time period to give the result. To effectively identify the species and evaluate resistance development, rapid, and quite exact technique like enzyme-linked immunosorbent assays must be employed in combination with cultures. Any clinical indication of fungus should be evaluated, and antifungal treatment should be given as early as possible (Yasmin et al. 2021).

Surgical debridement

Low drug bioavailability to site of infection can be caused by thrombosis of blood vessels and angioinvasion. Even if there is a slight possibility of mucormycosis, individuals should be prepared and prioritized for surgery. Surgical debridement of infected site has been found to reduce death rates by a significant amount (Spellberg and Ibrahim 2010). The MRI/CT-guided endoscopic sinus technique must be used to remove the afflicted tissue. Orbital exenteration and aggressive paranasal sinus debridement should be used to handle a rapid invasion of orbits (less than 72 h). Individuals should continue to receive intravenous AMB before beginning step-down therapy. Triazoles should be used to treat refractory infections. In the highly immunocompromised patients, it is preferable to take preventative measures to avoid immunosuppression before beginning antifungal treatment (Honavar 2021).

Iron chelators

The key function of metabolism of iron towards aetiology of mucormycosis suggests that potent iron chelators could be used as supplement to antifungal therapy. In fact, *R. oryzae* has been tested in vitro with two experimental iron chelators (Brunet and Rammaert 2020). The iron chelators like deferiprone and deferasirox did not permit the pathogen to absorb iron and presents an obstacle in development of micomycosis.

Novel therapies

In the recent years, the development of novel perspectives on the relationship that exists between the host, the fungus, and antifungal medication has been observed (lamoth and Kontoyiannis 2019). Some authors have emphasized PSZ's ability to accumulate inside the leukocyte membranes due to its lipophilic characteristics. PSZ was loaded into an HL-60 leukemia cell line that had been differentiated to a neutrophil-like phenotype and is also used in aspergillosis mouse model to distribute PSZ effectively into infectious area (Baistrocchi et al. 2017). This innovative approach, however, has not been evaluated against Mucorales. There has been significant advancement in bioengineering, particularly in the field of genetically engineered cytotoxic T-cells. The beta-glucan in the fungus cell wall can be specifically targeted by these modified T-cells (Baistrocchi et al. 2017). However, only an aspergillosis model has been used to test

Table 2 Summary of patents literature related to mucormycosis

Patent name	Patent number	Applicant	Publication date	Reference
An innovative portable handheld IOT enabled device for the identification of mucormycosis infected images considering the symptom severity for the focused treatment of patients	IN202241041139	Senthil Velan Suganantham C. Sugunadevi Sam Gilvine Samuvel CMR Institute of Technology	29.07.2022	(Suganantham et al. 2022)
A systematic model to detect black fungus appeared during COVID -19 using 3D convolutional neural networks	IN202211042624	Career Point University Kota	29.07.2022	(Hussain et al. 2022)
Kit and method for detecting mucormycosis pathogens	CN114574609	Guangdong Runpeng Biotechnology Co., Ltd	03.06.2022	(Chaojie et al. 2022)
Inhibitory potential of resveratrol and its natural analogues against RNA dependant RNA polymerase (RDRP) of rhizopus oryzae in mucormycosis through in silico investigations	IN202221008681	Mithun Rudrapal Ismail Celik Sampath Chinnam	11.03.2022	(Rudrapal et al. 2022)
Mucormycosis treatment agent	JP2021134176	Univ Chiba Nat Univ Corp Drug Genomics Co Ltd	13.09.2021	(Hiroharu 2021)
Novel fungal toxins and methods related to the same	US20210179695	Los Angeles Biomedical Research Institute at Harbor-Ucla Medical Center	17.06.2021	(Ibrahim et al. 2021)
Antifungal macrocyclic polyene novel compound	CN112175029	Liu Li	05.01.2021	(Liu 2021)
Methods of treating or preventing mucormycosis	WO2020006438	University of Maryland, Baltimore Los Angeles Biomedical Research Institute at Harborat [US]/[US]; UCLA Medical Center 1124 Carson Torrance, CA 90502, US; Los Angeles Biomedical Research Institute at Harborat [US]/[US]	02.01.2020	Bruno et al. 2020
Immunotherapy and diagnosis of mucormycosis using coth	US20190194301	Los Angeles Biomedical Research Institute at Harbor-Ucla Medical Center	27.06.2019	(Ibrahim et al. 2019a)
Fungal toxins and methods related to the same	US20190265238	Los Angeles Biomedical Research Institute at Harbor-Ucla Medical Center	29.08.2019	(Ibrahim et al. 2019b)
Method for inoculating fermented bean curd blank	CN110089577	Zhejiang University	06.08.2019	(Yuanming et al. 2019)
Volatile metabolite profiles for the diagnosis and treatment of mucorales fungi	US20190183887	The Brigham and Women's Hospital, Inc	20.06.2019	(Koo and Marty 2019)

Table 3 An outline of ongoing clinical trials invesigations of mucormycosis

Study title	Sponsor	Study type/allocation/intervention model	NCT no	Phase
Combined inhalational with intravenous Amphotericin B versus intravenous Amphotericin B alone for pulmonary mucormycosis	Postgraduate Institute of Medical Education and Research	Interventional/randomized/parallel assignment	NCT04502381	Phase 2
The Deferasirox-AmBisome therapy for mucormycosis (DEFEAT Mucor) study	Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center	Interventional/Randomized/Parallel assignment	NCT00419770	Phase 2
A study to evaluate isavuconazonium sulfate for the treatment of invasive aspergillosis (IA) or invasive mucormycosis (IM) in pediatric participants	Astellas Pharma Global Development, Inc	Interventional/non-randomized/single group assignment	NCT03816176	Phase 2
Pilot study of high dose liposomal Amphotericin B efficacy in initial zygomycosis treatment (AMBI-ZYGO)	Assistance Publique—Hôpitaux de Paris	Interventional/NA/single group assignment	NCT00467883	Phase 2
PK/PD study of Posaconazole for empiric treatment of invasive fungal infections in neutropenic patients or treatment of refractory invasive fungal infections (Study P01893)	Merck Sharp & Dohme Corp	Interventional/randomized/parallel assignment	NCT00034671	Phase 2
Clinical study of AK1820 (isavuconazonium sulfate) for the treatment of deep mycosis	Asahi Kasei Pharma Corporation	Interventional/randomized/parallel assignment	NCT03471988	Phase 3

this approach. CotH3, a Mucorales peptide that binds the human endothelial cell receptor GRP78, has recently been referred to mucormycosis endothelial invasion. Anti-CotH3 antibodies have prevented mucormycosis in neutropenic and diabetic mice and worked effectively in conjunction with antifungal agents (Gebremariam et al. 2019). Furthermore, other researchers have discovered that blocking the GRP78 cell receptor with GRP78-specific immune serum might help to protect diabetic mice from mucormycosis infection (Brunet and Rammaert 2020; Rocamora-Reverte et al. 2022). The interaction of this peptide-receptor could be a promising novel therapeutic avenue to investigate.

Nutraceuticals may play a vital role in the treatment of COVID-19. Natural compounds such as theaflavin, gallic acid, berberine, nimbin, curcumin, withaferin A, andrographolide, naringenin, mangiferin, luteolin, quercetin, piperine, resveratrol, and zingiberene bind to ACE-2 receptors and prevent the SARS-CoV-2 virus from attaching to host cell (Kunnumakkara et al. 2021; Maurya et al. 2020). The plant species with anti-inflammatory properties can be effectively used to decrease cytokine storm in COVID-19 individuals (Agnihotri et al. 2021; Kunnumakkara et al. 2021). Diet may be able to reduce inflammation, and also, nutraceutical may be proficient in stopping viruses from entering inside the body. Dietary nutraceuticals could be assessed as a complementary dimension in the management of CAM.

Patents and clinical status of in-progress treatment strategies for mucormycosis

From 2019 to 2022, patent and related data were searched on the World Intellectual Property Organization's official website using analytics to assess and organize current work related to mucormycosis (Table 2). Clinical trials have been conducted to evaluate the novel treatment for mucormycosis. In order to address the current treatment challenges, clinical trials on novel antifungal drugs and combinations of conventional agents are important. For better therapeutic recommendations, definitive clinical data from randomized prospective and observational research will be useful. Various clinical trials related to treatment approaches of mucormycosis are under different stages and few of them are enlisted in Table 3.

Conclusions and future prospectives

Mucormycosis (black fungus) is a deadly opportunistic illness that mostly manifests as a rhino-orbito-cerebral infection. According to studies, the life-threatening CAM is becoming more common in both COVID-19 infected as well as recovered patients all around the world. It was discovered

that, due to a severe shortage of sterile oxygen in few countries, a quick production of industrial oxygen is provided to save the patient, allowing pathogens of mucormycosis to enter immunocompromised patients, causing them to contract black fungus in addition to COVID-19. As a direct consequence of this, therapy and diagnosis of COVID-19 patients become challenging. People who take Deferoxamine, an iron overload treatment are quite susceptible to get black fungus. The diabetic individual's who have undergone treatment for COVID-19; a significant raise in CAM cases is linked with use of systemic corticosteroids which leads to immunosuppression. SARS-CoV-2 insulin resistance via the cytokine flow must be investigated as a separate risk factor for CAM because it causes immunosuppression. Due to quick development and angioinvasive nature of mucormycosis, prompt diagnosis and treatment should be started whenever it is suspected. Therefore, a high index of suspicion, initial diagnosis, stringent glycemic management, and avoidance from corticosteroids are all recommended. The physicians and healthcare professionals must be aware of implications of invasive supplementary mycotic infections in patients having COVID-19, particularly in those with already existing underlying conditions and comorbidities, and be able to detect and treat them immediately in order to reduce mortality and morbidity. Since then, Amphotericin B has been widely used for treatment, but Posaconazole and Caspofungin in combination have been proved to be efficacious due to possible synergistic action. As of now, the standard of care is immediate radical surgical debridement, lipid-based AMB, and Posaconazole. The promising future prospects for diagnosis and treatment of mucormycosis might emphasize upon rapid progression in chip-based sensors or implanted biosensors for active tracking of fungal analyte throughout the course of therapeutic intervention. In addition, to address the quick detection challenge of mucormycosis, the emerging biosensor devices could be developed by integrating particular molecular biological markers or species-specific identification elements. The current difficulties associated with infection necessitate clinical investigations of novel antifungal medications and combinations of existing antifungal treatments. The investigation of immune-boosting dietary nutraceutical that modify metabolic irregularities could be promising approach for management of COVID-19-associated mucormycosis.

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Declarations

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