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Review article

COVID-19 associated mucormycosis and their therapeutics

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ABSTRACT

Mucormycosis has spread rapidly in the COVID-19 and post-COVID-19 patients having low immunity and co-morbidities. It is also related to excessive use of corticosteroids, immunosuppressants, antibiotics, and unhygienic conditions. The efforts have been made to treat COVID-19 and post-COVID-19 associated mucormycosis. The first line of therapy includes liposomal amphotericin B, amphotericin B lipid complex and amphotericin B deoxycholate, while posaconazole and isavuconazole were effective as a second line of therapy. Notably, surgical debridement is an essential step in the treatment and is usually used along with antifungal therapy in the first line of treatment.

We have discussed COVID-19 and post-COVID-19 associated mucormycosis patients along with their co-morbidities and treatments. The discussion also included the role of iron and zinc in COVID-19 associated mucormycosis (CAM), mechanism of COVID-19 associated mucormycosis (CAM), its clinical trials, therapeutics of COVID-19 associated mucormycosis (CAM) involving liposomal amphotericin B (LAmB), Amphotericin B and mechanism of their action, mechanism of action of Azoles, different types of Covid-19 associated mucormycosis (CAM) patients including those having pulmonary mucormycosis, rhino-cerebral mucormycosis, cutaneous mucormycosis, rhino-orbital mucormycosis, gastrointestinal mucormycosis and sino-orbital mucormycosis and their therapeutics and surgical management of mucormycosis.

Furthermore, a clean, hygienic, and healthy environment should be maintained to avoid COVID-19 and post-COVID-19 associated mucormycosis. The early detection of COVID-19 associated mucormycosis (CAM) and post-COVID-19 associated mucormycosis determines the patients' outcome. The early diagnosis of post-COVID-19 associated mucormycosis can be achieved by following up COVID-19 patients who had previously received corticosteroids as COVID-19 treatment. Thus, early detection and treatment of COVID-19 associated mucormycosis (CAM) and post-COVID-19-associated mucormycosis may help control the high mortality rate and facilitate better management.

1. Introduction

COVID-19 pandemic is responsible for several hundred thousand deaths [1]. The SARS-CoV-2 virus enters human cells through angiotensin-converting enzyme 2 (ACE2) receptors, causing widespread cellular damage [2,3]. Alveolar damage, thrombosis, immune

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cell depletion and haemo phagocytosis have been reported in the autopsy of severe COVID-19 patients. Further, diseases such as mucormycosis, pancreatitis, adrenal micro infarction and pericarditis have also been observed in the autopsy of COVID-19 patients [4]. In the immunocompromised COVID-19 patients with co-morbidities such as diabetes, there are higher chances of invasive fungal infection, including aspergillosis, candidiasis, mucormycosis, or cryptococcosis [5].

Mucormycosis is an opportunistic and aggressive infection caused by mucor molds "mucoromycetes" that belong to the order of Mucorales and phylum *Mucormycota* [6]. The common causative agents responsible for mucormycosis infections are *Rhizopus, Lichtheimia, Apophysomyces, Mucor*, *Rhizomucor* species and sometimes also caused by *Cunninghamella* and *Saksenaea* species [7–9]. Mucorales are ubiquitously thermo-tolerant fungi whose distribution is different in the world, such as *Rhizopus arrhizus, which* is common in India and France, while *Cunninghamella* sp is common in Spain [9]. Recently, mucormycosis was inaccurately called "Black Fungus"; however, the fungi that cause mucormycosis have different colours [10].

COVID-19 associated mucormycosis (CAM) is caused by different *Rhizopus* sp. including *Rhizopus arrhizus, Rhizopus microspores, Rhizopus azygosporus, and Rhizopus oryzae* [11–17]. Further, mucormycosis was also reported by *Lichteimia* (Absidia) sp. Notably, co-infection with COVID-19 associated mucormycosis was also reported including *Rhizopus arrhizus with Aspergillus fumigatus, Rhizopus microspores* with *Aspergillus fumigatus*, mucormycosis with *Staphylococcus aureus* and yeast [11,12,18,19]. In the majority of mucormycosis related COVID-19 cases, diabetes was one of the reported co-morbidities, while mucormycosis was also reported in non-diabetic 67-year old male. However, mucormycosis with aspergillosis was also reported in non-diabetic 45-year old male [16]. *Rhizopus* microspores were further reported in end-stage kidney disease with diabetic patients and also in acute myeloid leukemia patients [13,17].

During the COVID-19 outbreak, there has been an increase in mucormycosis. It is a life-threatening disease in immunocompromised COVID-19 patients (Figs. 1 and 2). The fungal spores germinate to form hyphae that invade blood vessels and surrounding tissues, obstructing blood flow and resulting in tissue necrosis. According to WHO, mucormycosis incidents are rare and happen in 0.005 to 1.7 per million populations globally during normal time, while in India, the prevalence of mucormycosis was estimated to be 140 per million populations [20,21]. Kasatwar et al. [22] studied Coronavirus Associated Mucormycosis characteristics in India and suggested the prevalence of Coronavirus Associated Mucormycosis was 2300/million in COVID-19 infections. Further, it was about 10-fold higher when compared with the prevalence of mucormycosis in transplant recipients [22]. Notably, it has increased drastically during COVID-19 due to the compromised host's immune system.

Mucormycosis occurs in both active and recovered cases of COVID-19 patients, especially in those who are diabetic and are taking corticosteroids (Figs. 3 and 4). Notably, about 70% of rhino-orbital-cerebral mucormycosis cases are observed in diabetes patients with ketoacidosis. Cutaneous or subcutaneous mucormycosis has mostly occurred after trauma [23]. Rhino-orbito-cerebral mucormycosis (ROCM) and pulmonary mucormycosis have also occurred in patients with cancer chemotherapy or immunotherapy, hematological stem cell transplants, solid organ transplants, immunosuppressive patients taking corticosteroid treatment, and neutropenic patients [9,23,24].

Mucormycosis infects the upper respiratory tract, lung, eye, mouth, brain and skin causing blackening and further damage to the

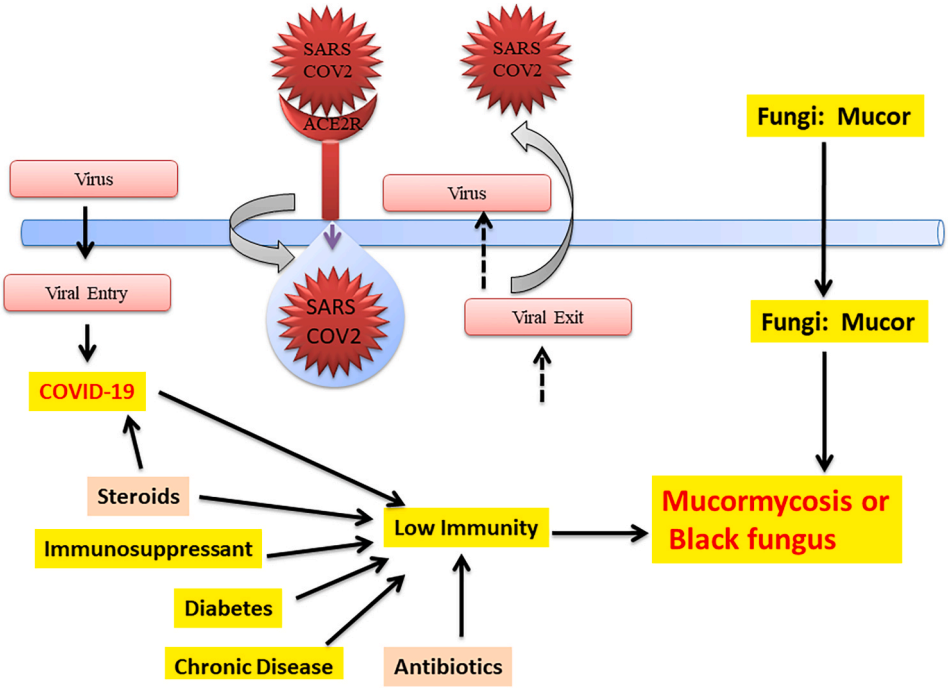

Fig. 1. Schematic representation of Covid-19 associated mucormycosis.

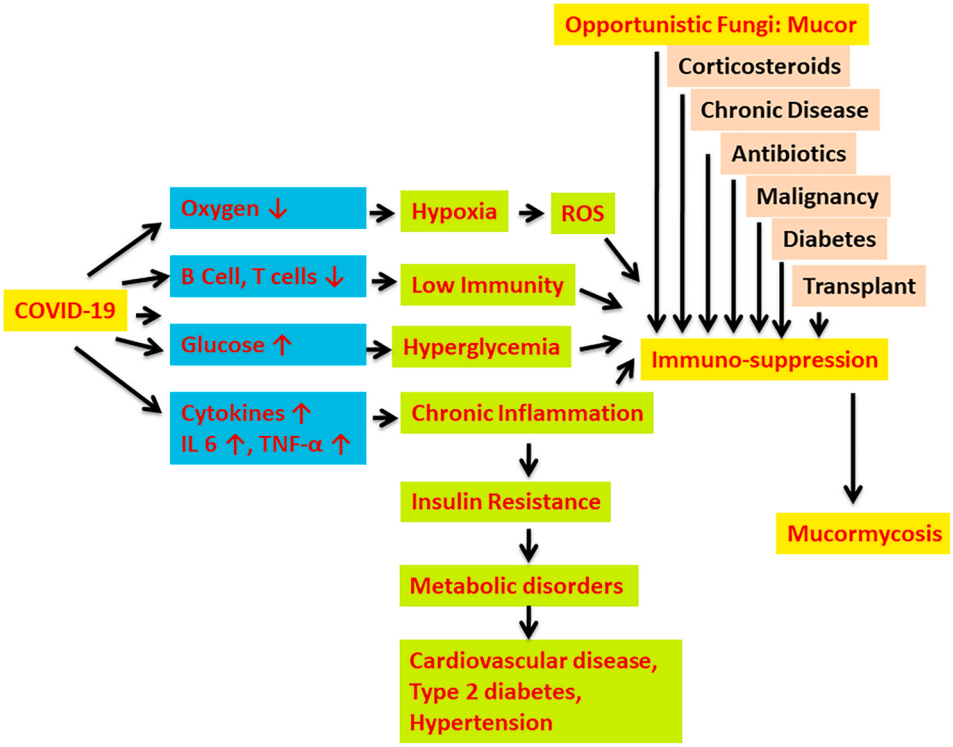

Fig. 2. Consequences of COVID-19 in human resulting in favorable condition for mucormycosis.

infected organs, but it is not contagious. Fungal spores enter into the upper respiratory tract during inhalation and cause disease in the susceptible host. The early sign of COVID-19 associated mucormycosis (CAM) involves fever, dyspnea, headache, coughing, bloody vomit, pain, and redness around the eyes and/or nose, altered mental status. The symptoms change according to the system being affected [25–27]. The unilateral facial pain or swelling, orbital swelling, or proptosis are also early symptoms of mucormycosis, while tissue necrosis is a late symptom [19]. Notably, nose-sinus and rhino-orbital are the most susceptible for mucormycosis in COVID-19 patients [28].

This review adds new value to the previous literature by summarizing the existing literature providing comprehensive review on the pathogenesis, and drug therapy in COVID-19 associated mucormycosis (CAM), different types of COVID-19 associated mucormycosis (CAM) patients and their therapeutics, mucormycosis in COVID-19 and post-COVID-19 patients with metabolic disorders, surgical management of mucormycosis, role of iron and zinc in CAM, clinical reports/trials including recent randomized controlled trials, thereby providing a conceptual framework and critical analysis that advances the field of COVID-19 associated mucormycosis (CAM) and their therapeutics. Further, it includes unique perspectives or insights by offering a more cohesive synthesis of current knowledge, including identification of knowledge gaps that would guide future research and public health strategies, and also proposals for future research directions. This review will enhance therapeutic strategies and improve quality-of-life outcomes in CAM patients.

2. Role of iron and zinc in COVID-19 associated mucormycosis

The chance of SARS-CoV-2 infected patients having mucormycosis increases due to several factors, including extensive use of steroids, iron, zinc supplements, low immunity, and co-morbidities [29]. Iron and zinc are among the most abundant transition metals present in cells and are also involved in COVID-19 associated mucormycosis (CAM). Iron and zinc minerals not only favor mucorales, but also other filamentous fungi including different species of *Aspergillus*. Mucorales and *A. fumigatus* are the major species causing co-infection with COVID-19, which may be due to local climatic conditions. The uptake of iron is important in the pathogenesis of mucormycosis [30,31]. There is an increase in the level of available serum iron in patients with hyperglycemia, diabetic ketoacidosis (DKA), and those having treatment with deferoxamine, which helps in the growth of mucorales in serum [6].

The level of ferritin is increased in COVID-19 patients, and this increases the susceptibility towards mucormycosis [32–34]. Hyperferritinemia is one of the important prognostic and diagnostic biomarkers for COVID-19 disease [8]. Further, the increase of serum ferritin is also an important manifestation in inflammatory reactions caused by COVID-19, which plays an important role in cytokine storms [35]. Hyperferritinemia and inflammation were responsible for the dysregulation of iron homeostasis in COVID-19 patients [36]. Further, hyperferritinemia causes hepatic cell death, apoptosis and is responsible for the release of serum ferritin and intracellularly stored free iron to the cell exterior. Unfortunately, opportunistic fungus like *R. oryzae* utilize a high level of free iron for

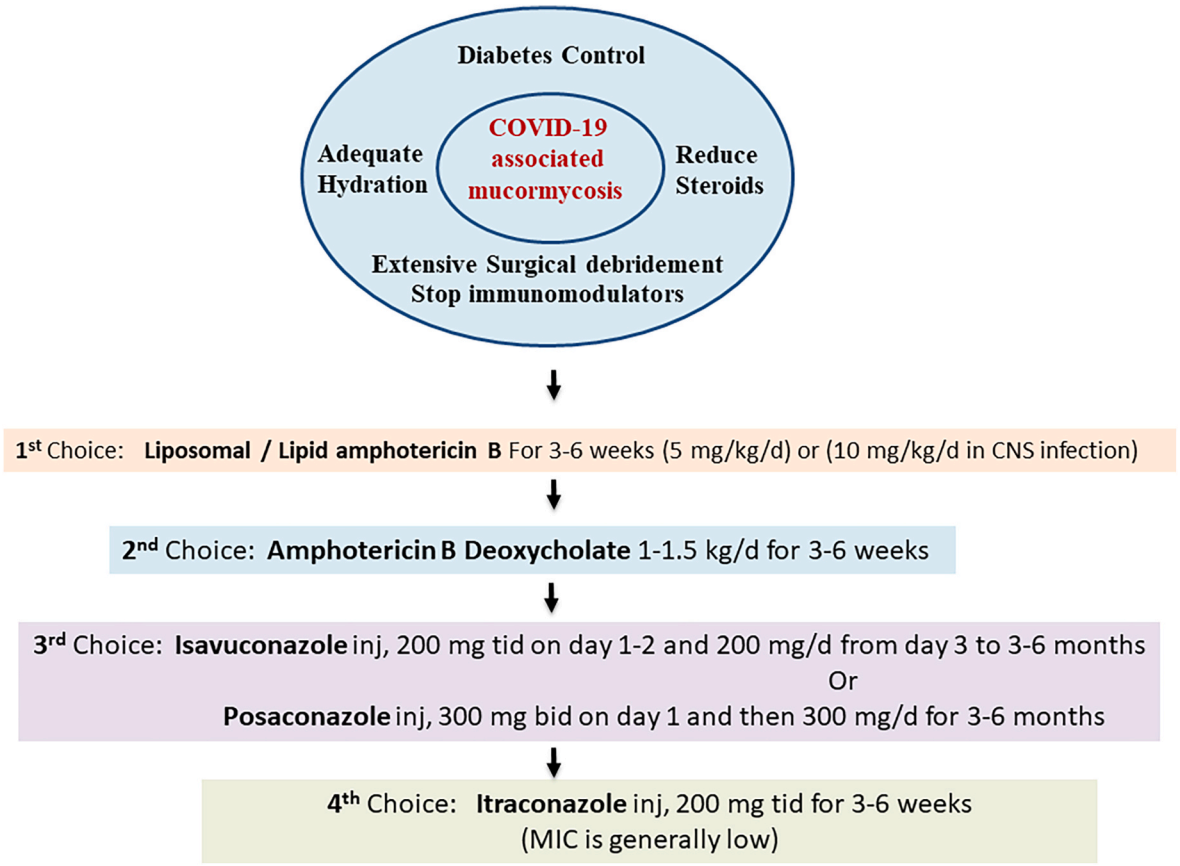

Fig. 3. Choices of therapeutics for COVID-19 associated mucormycosis infection.

fungal proliferation and growth (Fig. 4). Further, inflammation causes an imbalance of hepcidin (Fig. 4), an iron regulatory hormone that is also responsible for the increase of free iron levels in COVID-19 patients [37]. Further SARS-CoV-2 infection is responsible for the initiation of the 1-beta chain of hemoglobin that causes dissociation of porphyrins from iron and rapid discharge of high amounts of iron into circulation [8,38–40].

Notably, hyperferritinemia is not necessarily a parameter for iron overload [41]. In viral infections, including SARS-CoV-2 infection, or bacterial infections or inflammatory diseases, high serum ferritin is also generated by non-iron overload conditions [41]. The classification of hyperferritinemia included >1.5 × ULN (upper limit of normal)–500 ng/mL of serum ferritin values as mild increase, >500–3000 ng/mL of serum ferritin values as moderate increase and 3000−>100,000 ng/mL of serum ferritin values as marked increase [41]. Interestingly, serum iron concentration, transferrin saturation, and liver MRI (magnetic resonance imaging) are useful in differentiating between non-iron overload hyperferritinemia and iron overload hyperferritinemia [41]. A significantly high serum ferritin level was observed in severe and critical groups of COVID-19 patients compared to the mild and moderate groups of COVID-19 patients. Further, significantly high serum ferritin was reported in dead COVID-19 patients compared to surviving patients of COVID-19 disease. The cutoff value of 635.25 ng/ml, identified by Youden's index was observed in patients with severe COVID-19 disease (with 76% sensitivity and 90.5% specificity). In comparison, the cutoff value of 760.65 ng/ml was observed to predict the mortality of patients with COVID-19 disease (with 73.3% sensitivity and 84.1% specificity) [42]. Deng et al. [43] have observed median ferritin concentration is significantly three times higher in the death/non-survival group of COVID-19 compared to the survival group of COVID-19 (1722.25 μg/L vs. 501.90 μg/L, $p < 0.01$) [43].

Zinc is also important in fungal pathogenies and may increase the *Rhizopus* growth [7,44,45]. Zinc has the potential to promote *in vitro* growth of isolates of *Rhizopus arrhizus* from COVID-19 associated mucormycosis (CAM). Further, a significant increase in fungal biomass in the presence of zinc may cause mucormycosis despite having a normal immune function. Muthu et al. [46], reported isolates of *Rhizopus arrhizus* from COVID-19 associated mucormycosis (CAM). patients who had high growth in zinc enriched culture media for fungi. Further, viable count percentage suggested a significant increase of growth in 4 out of 8 isolates of *Rhizopus arrhizus* from COVID-19 associated mucormycosis (CAM) and were observed in zinc enriched culture media. It had both an increase in colony count and larger colonies. Further, in all 3 tested isolates of *Rhizopus arrhizus,* the increase in the mean fungal biomass with zinc was also observed in a time-and concentration-dependent manner [46]. Further, high and increasing doses of zinc concentration were unable to increase the colony numbers. Notably, serum zinc levels had no significant difference in COVID-19 associated mucormycosis (CAM) cases, and COVID-19 controls showed no conclusive evidence about the role of zinc in favoring or not favoring mucormycosis.

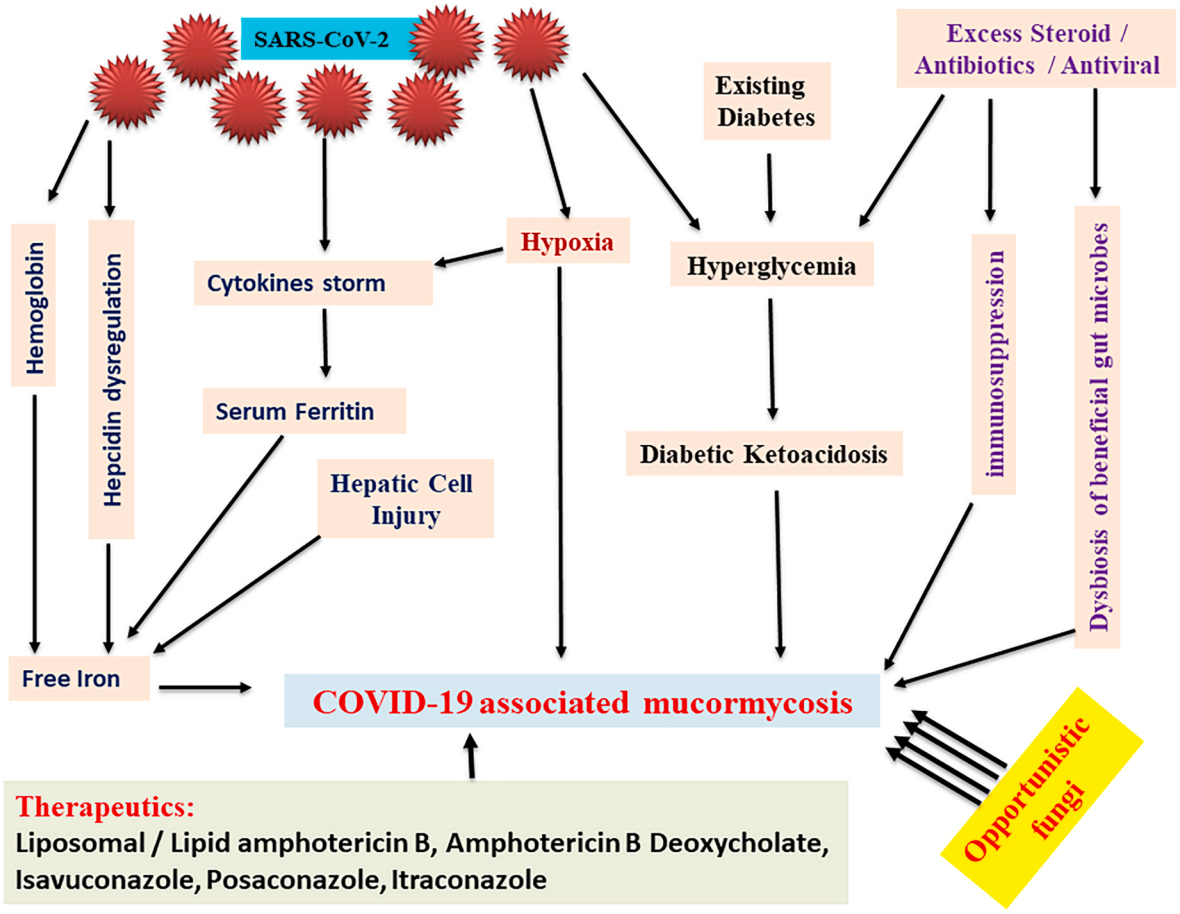

Fig. 4. Signaling pathways involved in creating favorable environment for COVID-19 associated mucormycosis.

Thus, the role of zinc level in mucormycosis is still under investigation. However, the increased level of zinc may play a role in spreading mucormycosis in COVID-19 patients.

3. Mechanistic and therapeutic details of COVID-19 associated mucormycosis

3.1. Mechanism of COVID-19 associated mucormycosis

The SARS-CoV-2 infection causes a significant reduction in the number of T lymphocytes, including $CD4^+$ and $CD8^+$ T cells, causing lymphopenia or lymphocytopenia, thereby resulting in a high risk of infection from mucormycosis (Figs. 1 and 2) [47]. SARS-CoV-2 causes excessive production of pro-inflammatory cytokines, including hyperproduction of IL-1, IL-6, IL-12, IFN-γ, and TNF-α, which damages the lung cells. Interestingly, tocilizumab targets IL-6, azithromycin targets IL-6 and TNF-α, certolizumab targets TNF-α and these are now used for the COVID-19 treatment [48].

Chronic inflammation causes insulin resistance by impairing the insulin signaling pathway in adipocytes and further leads to several metabolic disorders, including cardiovascular disorders, hypertension, and diabetes [49]. COVID-19 may lead to reduced oxygen levels, resulting in hypoxia and increased production of reactive oxygen species (ROS). Further, COVID-19 induces hyperglycemia [50] and makes glycemic control difficult, thereby creating a favorable environment for mucormycosis. (Figs. 2 and 4). COVID-19 causes hyperferritinemia; elevated ferritin levels are responsible for the surplus intracellular iron, which produces ROS and damages the tissue [29]. Interaction of labile Fe^{2+} with hydrogen peroxide (H_2O_2) generates reactive oxygen species or lipid peroxides, leading to hepatic cell death and extracellular release of labile iron and serum ferritin [8]. IL-6 triggers ferritin production and elevates the synthesis of hepcidin that confiscates iron in enterocytes and macrophages to prevent them to efflux from these cells, thereby enhancing intracellular iron load. Further, this surplus intracellular iron generates ROS that is responsible for tissue damage (Fig. 4). Further, the release of free iron in circulation is utilized by mucorales [9].

Potenza et al. [51] have reported that mucorales specific T cells were detected in invasive mucormycosis (IM) hematological patients during treatment, however, it was not detected before the treatment and after the cure. Mucorales specific T cells were producing different cytokines mainly IL-4, IL-10, and IFN-γ, and also IL-17, which belonged to $CD4^+$ and $CD8^+$ groups. Notably, these

cytokines, especially IFN-γ producing T cells were able to harm and directly damage the mucorales hyphae [51]. Liu et al. [52] have studied peripheral blood and reported a significant decrease in the count of lymphocytes, T cells, especially $CD8^+$ T cells, along with an increase in the counts of neutrophils, IL-6, IL-10, IL-2 and IFN-γ levels were observed in the case of severe COVID-19 patients compared to mild COVID-19 patients [52]. Further, neutrophil-to-lymphocyte ratio (NLR) and neutrophil-to-$CD8^+$ T cell ratio (N8R) with AUC = 0·93 and AUC = 0·94 can be used as a marker for the severity of COVID-19 as it is dynamically correlated with mucormycosis [52].

3.2. Clinical trials

Large multicentric and regional studies consistently identify diabetes and usage of corticosteroids as the predominant risk factors for COVID-19 associated mucormycosis (CAM). In a worldwide study of 958 COVID-19 associated mucormycosis (CAM) cases from 45 countries, mainly with 844 cases of CAM from low or middle-income regions, Ozbek et al. [53] reported a mortality of 38.9% (303/780) patients. Corticosteroid usage was documented in 78.5% (619/789) of patients, while diabetes was present in 77.9% (738/948) of patients. CAM typically developed at a mean of 8 days after hospitalization and approximately 22 days after COVID-19 diagnosis. Advanced age, multiple co-morbidities, Aspergillus co-infection, and tocilizumab therapy further increased risk [53].

Similar findings were reported in smaller cohorts. Hussain et al. [54], in a cohort of 167 CAM patients, reported a mortality rate of 38.3%, with better survival (64.96%) among those receiving combined surgical and medical management. Diabetes (73.6%), hypertension (22.8%), and renal failure (10.8%) were the most frequent comorbidities. Common clinical manifestations among CAM patients included facial pain, ptosis, proptosis, reduced visual acuity, and vision loss [54]. An oral and maxillofacial surgery (OMFS) based study involving 28 CAM patients found diabetes as a major co-morbidity in 27 cases, followed by hypertension in 8 cases. Some patients had oxygen and steroid therapy. Reported cases of mucormycosis were mainly 10–14 days or more than 15 days gap after COVID-19 recovery [55].

Indian studies reinforce these observations. The clinical profile of 115 patients affected with CAM from various parts of India was studied, and it was found that corticosteroids were administered in all patients, and 85.2% of patients had diabetes, including 13.9 % were newly diagnosed diabetic cases. Rhino-orbital involvement was the predominant presentation of mucormycosis, with an overall mortality of 21.7% [56]. Observational study with 70 CAM patients [57], 131 Acute Invasive Fungal Rhinosinusitis patients in a COVID hospital in Delhi identified diabetes, steroid usage for COVID-19, uncontrolled diabetes, and improper usage of corticosteroids as major risk factors for this disease [57,58]. Notably, liposomal amphotericin B, posaconazole and voriconazole were used as medical management and surgical treatment [58]. Further, similar major risk factors like diabetes, history of COVID-19, uncontrolled diabetes, positive COVID-19, steroids usage, diabetic ketoacidosis [59,60] were also found in case-control studies from tertiary care centers in Bhopal with 168 cases of mucormycosis [59] and in a tertiary care hospital in North India with 109 patients with suspected/confirmed mucormycosis [60]. Notably, rhino-orbital (34.8%), rhino-orbital cerebral (20.18%), and pulmonary (23.8%) mucormycosis were the most frequent clinical forms [60]. Comparable trends were also observed during the third wave of COVID-19 in Pakistan, where a tertiary care hospital reported 43 cases of mucormycosis, out of which only 22 cases had a history of COVID-19, with diabetes as a dominant co-morbidity, and all CAM patients had a history of corticosteroid usage [61].

Randomized clinical trials evaluating CAM management remain limited, particularly for pulmonary mucormycosis. A randomized controlled trial (NCT04502381) compared intravenous liposomal amphotericin B alone versus its combination with adjunctive nebulized amphotericin B deoxycholate in 32 patients with pulmonary mucormycosis. Diabetes and COVID-19 were common underlying factors. While adjunctive nebulized therapy was safe, it did not significantly improve treatment outcomes at 6 weeks [62]. Another single-blinded randomized controlled trial conducted at All India Institute of Medical Sciences (AIIMS) Bhubaneswar (45 participants) demonstrated that postoperative application of liposomal Amphotericin-B gel reduced the need for revision surgery and facilitated early recovery in CAM patients when compared with conventional Povidone-Iodine and saline nasal douching [63].

Several observational and interventional trials across different countries have further examined CAM epidemiology, risk factors, complications, and outcomes. These include clinical trial studies in France (NCT04368221), Egypt (NCT05074043) and India (NCT04935463) [64–66]. Collectively, these trials focus on identifying predictors of CAM, patterns and complications of mucormycosis during COVID-19 or post COVID-19 treatment and its outcomes, vision loss in CAM, rhino-orbital mucormycosis in COVID-19 patients, management of Rhino-Orbito-Cerebral Mucormycosis in COVID-19 patients, ICU-related fungal infections, their preventive strategies and steroid usage in COVID-19 patients [64–66].

Overall, available evidence highlights CAM is associated with high morbidity, variable prognosis, and recurrence, necessitating early diagnosis, aggressive antifungal therapy, and prompt surgical debridement.

3.3. Therapeutics of COVID-19 associated mucormycosis

COVID-19 associated mucormycosis (CAM) may be treated using intravenous anti-fungal therapy and surgical excision, suggesting the need for a multidisciplinary medical team. Liposomal amphotericin B emerged as favorite drug of choice for COVID-19 associated mucormycosis (CAM) along with posaconazole, or isavuconazole. Treatment for COVID-19 associated mucormycosis (CAM) depends upon the patient's condition, early diagnosis, infection site, and immunosuppression. Early diagnosis and treatment of mucormycosis can reduce the mortality rate and also improve the outcome [67,68].

The Directorate General of Health Services (DGHS), India, has guidelines for the treatment of COVID-19 associated mucormycosis (CAM) in India. Liposomal Amphotericin B at a dose 5 mg/kg body weight should be the preferred choice for COVID-19 associated mucormycosis treatment while 10 mg/kg body weight may be given in case of CNS involvement. Further, it should be diluted in 5% or 10% dextrose because it is incompatible with normal saline/ringer lactate. After achieving a favorable response or stabilization of

disease in some weeks, following which step down to oral posaconazole (300 mg delayed release tablets twice a day for 1 day followed by 300 mg/d for 3-6 months in case of COVID-19 associated mucormycosis (CAM) (Fig. 3) or isavuconazole (200 mg 1 tablet 3 times daily for 2 days followed by 200 mg daily for 3-6 months) may be suggested [9,69]. A study reported that posaconazole in the CAM patient was initiated with an intravenous (IV) formulation at a dose of 300 mg twice a day, followed by the 300 mg gastro-resistant posaconazole tablet once per day [70]. Posaconazole has formulations such as an oral suspension, a delayed-release tablet, and an intravenous formulation [70].

Posaconazole or isavuconazole was suggested as maintenance therapy after their complete or partial response except in azoles resistant organism. The maintenance therapy continues for about 4 to 6 weeks and may be needed for a longer duration of up to 3 months. Further, the duration of maintenance treatment is required to be personalized on the basis of COVID-19 comorbidities, type of mucorales and coexisting illnesses. Salvage therapy with posaconazole or isavuconazole is suggested in the case of stable or progressive disease [71]. The delayed-release tablet of posaconazole was favored over the suspension form. The posaconazole was preferred over isavuconazole due to cost, availability and published evidence [71]. In a study reported by Mukherjee et al. [72] it was found that according to the stage of Rhino-Orbital-Cerebral Mucormycosis (ROCM), the oral posaconazole step-down therapy was continued for 3, 4 and 1/2 months, and also 6 months, it was also elongated for another 6 weeks depending on the active case. Notably, the posaconazole therapy was reported to be required utmost up to 7and1/2 months [72].

European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) had recommended liposomal/lipid amphotericin B for 3-6 weeks at a dose of 5 mg/kg/d or 10 mg/kg/d in case of CNS infection. Amphotericin B Deoxycholate had been recommended at a dose of 1-1.5 kg/d for 3-6 weeks (Fig. 3). [9]. Amphotericin B had been suggested as first-line therapy for mucormycosis, while posaconazole and isavuconazole were also effective in the absence of amphotericin B and are second-line therapy (Figs. 3 and 4). Amphotericin B is a polyene anti-fungal compound produced by *Streptomyces nodosus*, binding with ergosterol of fungal cell membrane, causing depolarization of fungal cell membrane and changes in the permeability of cell membrane. Notably, the transmembrane channel is formed that helps the potassium (K^+), sodium (Na^+) and other components to leak out of the fungal cell membrane, causing cell death. Further, it also produces oxygen radicals [28]. Notably, itraconazole had also shown anti mucorales activity *in vitro* [9]. Various amphotericin B formulations were available, such as liposomal amphotericin B, amphotericin B deoxycholate, amphotericin B lipid complex, amphotericin B colloidal dispersion, while liposomal amphotericin is the best choice [9]. Deferasirox, an iron chelator may be helpful with anti-fungal therapy for COVID-19 associated mucormycosis (CAM) patients having diabetes, while it can be avoided in hematological malignancy [24].

COVID-19 associated rhino-orbital-cerebral mucormycosis (CAROCM) is common in the ongoing pandemic followed by pulmonary mucormycosis [73]. Optimal use of corticosteroids and controlling diabetes is a major step to prevent mucormycosis. Further, early radiology-guided surgical intervention was needed to save the life. Orbital exenteration is required in the advanced stage of CAROCM patients [74].

The Orbital exenteration is the surgical removal of the eyeball along with the adnexa that is required in case of extensive orbital involvement in COVID 19 associated Rhino-orbital–mucormycosis. The indication for orbital exenteration includes significant proptosis with fulminant orbital involvement, extensive intraconal involvement in the lateral compartment, globe invasion, ineffective towards conservative surgery [75]. Maurya [76], suggested that the orbital exenteration may be considered only after careful consideration to save the life of ROCM patient with a highly inflamed orbit, a painful blind eye, a frozen eyeball, and severe orbital and CNS disease manifested [76]. In the advanced mucormycosis stage, extensive debridement of external infected tissues has been suggested and it can be repeated in the case of recurrence [9,73].

Most of the guidelines for the treatment of mucormycosis have suggested liposomal amphotericin B (AmB) as the preferred choice. Further, several adverse events were reported for AmB including acute renal injury, increased levels of creatinine in blood, renal impairment, pyrexia, hypokalaemia, and multiorgan dysfunction syndrome [73,74]. To control the adverse effects during AmB treatment, there is a need to evaluate the renal function and potassium level. A dose reduction of 50% AmB had been recommended in case of renal impairment [73]. Isavuconazole or posaconazole can be used for mucormycosis as second-line therapy when patients are contraindicated to AmB.

Although itraconazole had also shown anti mucorales activity *in vitro* [9], however, itraconazole MIC is generally low. Further, the effect of itraconazole is limited against Mucor spp. Notably, itraconazole has been used against *M. irregularis* that causes cutaneous mucormycosis in case of intolerance to amphotericin B. Itraconazole is not recommended for the treatment and management of mucormycosis, while it may be used as intravenous therapy in the case of shortage of recommended antifungal for COVID-19 mucormycosis [77]. Dandu et al. [78] showed the potential role of oral Itraconazole in COVID-19-associated Rhino-orbito-cerebral mucormycosis (ROCM) patients. The 12 out of 14 patients had diabetes, 10 out of 14 patients had bilateral sinus, 13 out of 14 patients had orbital extension, 5 out of 14 patients had cavernous sinus, 3 out of 14 patients had cerebral part of the internal carotid artery, and 4 out of 14 patients had brain infarcts. Notably, all the 14 patients showed sensitivity to Itraconazole, with minimum inhibitory concentration (MIC) $\leq$ 1 μg/ml in 12 patients and MIC $\leq$2 μg/ml in 2 patients. Further, 11 out of 14 patients showed clinical improvement and 6 out of 7 scanned patients showed radiological improvement during 6 months of follow-up. Itraconazole is a safe, cheap, and effective treatment in sensitive cases [78].

Further, during treatment with itraconazole and posaconazole, monitoring was suggested at 5 and 7 days of treatments respectively. Oral fluconazole, oral prophylaxis with itraconazole and voriconazole had been suggested in mucormycosis patients with neutropenia or graft-versus-host-disease [79]. Azoles may be responsible for the enhancement of the colchicine and ruxolitinib exposure; in this situation, itraconazole-colchicine co-administration might be avoided. Further use of AmB with steroids may cause hypokalemia that needs optimal dose adjustments. Treatment choice for COVID-19 related mucormycosis is limited and is centered around AmB and azoles that may create economic difficulties in case of the requirement of a large number when the mass population

gets infected, thereby causing scarcity and unavailability of the medicines [80].

The requirement of the multidisciplinary team involving a microbiologist, neurology specialist, internal medicine expert, intensivist, ophthalmologist, dentist, otorhinolaryngologist, maxillofacial specialist, and biochemist to handle the COVID-19–associated mucormycosis patients has been suggested by the Indian Council for Medical Research (ICMR) [81].

3.3.1. Liposomal amphotericin B (LAmB), amphotericin B and mechanism of their action

Liposomal amphotericin B (LAmB) is a lipid formulation of amphotericin B and is one of the preferred choices for the treatment of opportunistic fungal pathogens, including mucormycosis, aspergillosis, candidiasis, cryptococcal meningitis and also for visceral leishmaniasis [82]. In the ongoing COVID-19 pandemic, liposomal amphotericin B has played an important role in the treatment of COVID-19 associated mucormycosis (CAM). Amphotericin B is retained in the liposome and after contact between the liposome and fungal, it detaches from the liposome and binds to ergosterol of the fungal membrane. LAmB has less nephrotoxicity and infusional toxicity compared to other available formulations of amphotericin B. Polyenes can remain in tissues for an extended period, which enhances their therapeutic effectiveness. The toxicity profile of LAmB is significantly improved compared to amphotericin B deoxycholate (DAmB) [82].

Amphotericin B (AmB) has properties to bind with ergosterol of the fungal cell membrane, causing pore formation, ion leakage, and finally fungal cell death. Notably, liposomes without AmB also bind to the fungal cell wall and do not cause rupture of the fungal cell wall, but the empty liposome and fungal cell wall remain intact. Fortunately, amphotericin B-containing liposomes bind to the fungal cell wall and cause fungal cell death, suggesting liposomal disruption and release of amphotericin B that finally binds to ergosterol of the fungal cell membrane [83]. The fungal cell wall has sterol present in the cell wall known as ergosterol, while the principal component of liposome is cholesterol [84]. Notably, amphotericin B has a higher binding affinity for ergosterol compared to cholesterol; therefore, liposome disruption occurred, and amphotericin B is released. This is further transferred to the cell membrane and exercises its anti-fungal activity by the formation of pores or transmembrane channels, a change in membrane permeability, ion leakage and causes fungal cell death [84]. Amphotericin B binds irreversibly to ergosterol of the fungal cell membrane. Fortunately, body temperature is very suitable for the transfer of amphotericin B from the liposome to the fungus [85].

LAmB has great properties to prolonged mean residence time in tissues that suggest without compromising efficacy it may be given intermittently, short course, or single-dose according to the situation of the patient. Further, it may help to decrease the cost, reduce the adverse events, and also may be used in ambulatory settings. LAmB showed a long terminal half-life in plasma. Further, higher amphotericin B was observed in plasma compared to amphotericin B deoxycholate. Notably, biologically active amphotericin B resulted only after the direct contact of LAmB with fungus [86]. LAmB showed less nephorotoxicity compared to other lipid formulations of amphotericin B including amphotericin B deoxycholate [87]. Renal toxicity may occur due to free or readily diffusible amphotericin B coming in contact with renal distal tubules while LAmB is encapsulated in liposome therefore unable to interact with various sub-compartments in the kidney. Additionally, no glomerular filtration occurred due to the size of liposomes that suggest lower renal toxicity of LAmB [88]. LAmB has lower toxicity compared to other polyene formulations including DAmB and amphotericin B lipid complex (ABLC) [89]. LAmB may cause deranged liver function tests while the mechanism of hepatotoxicity with LAmB still not known [90,91].

Mucormycosis is rare and devastating infection and commonly occurred by *Rhizopus* sp that preferably target immunosuppressed patients and patients with diabetic ketoacidosis (Fig. 4). The polyenes are the first line of therapeutics, such as LAmB, which is mostly used for mucormycosis [92].

Intra-orbital injection of amphotericin B: In a study, Murthy et al. [93] suggested that the amphotericin B injection into the orbit using an IV cannula, is a viable and simple treatment option for COVID-19-associated rhino-orbital mucormycosis. Further, the application of retrobulbar injection is to halt orbital progression, provide globe sparing, avoid exenteration and use to save the eyeball in ROCM patients [93]. Retrobulbar injection of amphotericin B may be considered safe, protective and an alternative intervention against orbital exenteration in COVID-19 Associated Orbital Mucormycosis patients [94].

Ramamurthy et al. [95] studied 82 eyes of post-COVID-19 ROCM and suggested the transcutaneous retrobulbar injection of amphotericin B (TRAMB) was an adequate and safe treatment in the mild to moderate ROCM and a good adjunct with other interventions in the severe cases [95]. In a study by Shakrawal et al. [96], they studied forty-four eyes of 42 patients of post-COVID-19 ROCM and suggested the TRAMB as an adjuvant therapy for COVID-19 ROCM to decrease the disease progression, stabilization of orbital involvement, help to preserve the globe or sight and as alternate to orbital exenterations [96].

Local irrigation of amphotericin B: Interestingly, a Rhino-orbital mucormycosis COVID-19 patient was denied orbital exenteration and the patient survived with systemic amphotericin B, daily endoscopic sinus debridement and irrigation with diluted amphotericin B [97]. Acharya et al. [98] reported a study where IV liposomal amphotericin B was administered in 25 COVID-19-Associated Rhino-Orbital Mucormycosis patient, while transcutaneous retro-orbital amphotericin B deoxycholate was received by 24 patients and amphotericin B irrigation of the wounds was done for all 25 patients. Further, alternate-day suction and amphotericin B nasal irrigation were performed in a surgical debridement patient [98]. Ramamurthy et al. [95] reported orbitotomy and debridement with amphotericin B irrigation in post-COVID-19 ROCM patients [95]. The Irrigation with amphotericin B (1 mg/ml) of orbit and sinuses helps in increasing the local concentration of the drug and provides better outcomes [99].

3.3.2. Mechanism of action of azoles

Isavuconzaole disturbs the synthesis of ergosterol by inhibiting cytochrome P450-dependent enzyme lanosterol 14α-demethylase that involve in the conversion of lanosterol to ergosterol and causes changes in the structure and function of the fungal membrane and ultimately cell death [100,101]. Isavuconazole injection had been recommended at a dose of 200 mg tid on day 1-2 and 200 mg/d from

day 3 to 3-6 months in case of COVID-19 associated mucormycosis (CAM) (Fig. 3) [9,69]. Posaconazole inhibits the cytochrome P-450 dependent enzyme, sterol 14α-demethylase of fungi by binding to its heme cofactor, which stops the synthesis of ergosterol and causes cell death. Posaconazole injection had been recommended at a dose of 300 mg bid on day 1 and 300 mg/d for 3-6 months in case of COVID-19 associated mucormycosis (CAM) (Fig. 3). [9,69]. Itraconazole inhibits the cytochrome P-450 enzyme 14-α demethylase and ceases the synthesis of ergosterol and finally causes cell death. Itraconazole injection had been recommended at a dose of 200 mg tid for 3 weeks itraconazole injection (Fig. 3). [9].

4. Types of COVID-19 associated mucormycosis patients and their therapeutics

4.1. Pulmonary mucormycosis

Pasero et al. have reported the first case of COVID-19 with mucormycosis in Italy in a 66-year old male COVID-19 patient developing cavitary pulmonary mucormycosis. SARS-CoV-2 infection may cause an alteration of the immune system and co-infection caused by opportunistic fungi Rhizopus species in lungs with significant parenchymal damage [47]. Another case was of a person admitted to a hospital in the USA with viral pneumonia and COVID-19 symptoms. Treatment had been done for COVID-19 with antibiotics, antiviral therapy, high-dose glucocorticoids, and interleukin antagonists. Later, bronchopleural fistula and mucormycosis were confirmed during the hospitalization. Further, it was confirmed that the lung parenchyma was invaded by mucormycosis with Rhizopus species. Immuno-compromised health was responsible for the development of mucormycosis and bronchopleural fistula [102]. In addition, Garg et al. have reported pulmonary mucormycosis in a 55-year-old male COVID-19 patient in India with diabetes and end-stage kidney disease. Mucormycosis was detected after 21 days of hospitalization of COVID-19 patients. A further cause of mucormycosis by *Rhizopus microsporus* was confirmed by Lactophenol cotton blue (LCB) mount and MALDI-TOF with a good discriminatory score of 2.1. Treatment of mucormycosis has been done using 5 g of liposomal amphotericin B and COVID-19 patient was discharged after 54 days from hospitalization [13].

4.2. Rhino-cerebral mucormycosis

Alekseyev et al. [103] have reported rhino-cerebral mucormycosis in a COVID-19 patient with type 1 diabetes mellitus in a 41-year-old man in the USA. The patient was treated with steroids and hydroxychloroquine. Further treatment with insulin drip, cefepime, IV abelcet (Amphotericin B lipid Complex), and three surgical debridements had been carried out successfully. In addition, the patient was prescribed anticoagulant coumadin and antifungal IV abelcet during his homestay [103].

***4.3**. Cutaneous mucormycosis*

A cutaneous mucormycosis was reported in a 68 year male COVID-19 patient in the USA with diabetes, a recent history of heart transplant recipient and was using immunosuppressive medication [15].

4.4. Rhino-orbital mucormycosis

A rhino-orbital mucormycosis was reported in both a 54-year old man and a 40-year old woman with severe COVID-19 in Iran. As part of COVID-19 treatment, these patients have received corticosteroids and were later treated with amphotericin B for rhino-orbital mucormycosis. One of the patients died due to intracranial space involvement, while the other was successfully treated [97]. Mekonnen et al. have reported a case of fatal acute invasive rhino-orbital mucormycosis in a 60-year old man in the USA infected with COVID-19 and had insulin-dependent diabetes, asthma, hypertension, and hyperlipidemia, Further, *Rhizopus* species was confirmed and treated with liposomal amphotericin B. The patient has been treated for COVID-19 with dexamethasone and convalescent plasma. Notably, dexamethasone was responsible for causing uncontrolled hyperglycemia with insulin usage. Further, the patient was transitioned to posaconazole from liposomal amphotericin B due to acute kidney injury [104]. A fatal rhino-orbital mucormycosis in a 24-year-old female with COVID-19 was reported in Mexico City with a past history of obesity. She has been treated with imipenem/linezolid and amphotericin B as empirical treatment [105].

4.5. Gastrointestinal mucormycosis

A fatal gastrointestinal mucormycosis was found in an 86-year-old male COVID-19 patient in Brazil with a history of arterial hypertension. He received the treatment of ceftriaxone, azithromycin, oseltamivir, and hydrocortisone. He developed melena and severe anemia. Esophagogastroduodenoscopy (EGD) discovered two big gastric ulcers with necrotic debris and a deep hemorrhagic base. The biopsies confirmed the presence of gastrointestinal mucormycosis [106].

4.6. Sino-orbital mucormycosis

Maini et al. [107] have reported post-COVID-19 infection of sino-orbital mucormycosis in a 38-year-old male in India caused by *Rhizopus oryzae*. On the 18th day of his COVID-19 recovery, the patient had developed pain in the left eye and chemosis was confirmed by magnetic resonance imaging (MRI) and functional endoscopic sinus surgery. The treatment with fluconazole, amphotericin B and

surgical debridement helped the patient to recover from mucormycosis with some residual deformity [107]. Fluconazole was used against white fungi such as Candida sp. and amphotericin B was used against mucormycosis such as *Rhizopus sp* [107].

5. Mucormycosis in COVID-19 and post-COVID-19 patients with metabolic disorders

A high number of COVID-19 infections in diabetic patients is making way for mucormycosis. John et al. have reviewed 41 cases of mucormycosis associated with COVID-19 and observed that a majority of cases are related to diabetes mellitus with severe or critical COVID-19. Poorly controlled diabetic patients were at risk for mucormycosis. Most of the cases have been reported in males, and the affected organs were rhino-orbital or rhino-cerebral in diabetes patients [108]. Another study by Moorthy et al. reported 16 cases of mucormycosis in India. The majority of mucormycosis patients were diabetic and infected with COVID-19 earlier and had used steroids for COVID-19 treatment. All the patients had sinusitis, and the majority of patients reported a loss of vision, and maxillary necrosis [18].

Sharma et al. [109] have reported that 23 patients (15 males and 8 females) in India with mucormycosis were related to COVID-19 and were administered steroids during their treatment. Notably, four patients were COVID-19 infected, while 19 patients had a history of COVID-19. Within them, 14 patients had diabetes and hypertension, while 7 patients had only diabetes. The infection was reported in the ethmoid group of sinus air cells and also in the maxillary sinus. It was found that about 10 patients were related to intra-orbital infections [109]. The study suggested that mucormycosis was occurring in both COVID-19 and post-COVID-19 patients.

6. Surgical management of mucormycosis

The mucormycosis treatments require both well synchronized surgical and medical approach. Notably, the surgical debridement is required to remove the devitalized tissue. The COVID-19 associated mucormycosis (CAM) impacts the sinuses in the majority of cases followed by the rhino-orbital cerebral region. The surgical intervention is important due to the poor penetration of antifungal agents at the infection site because of the thrombosis of blood vessel and tissue necrosis [110].

The surgery had significantly better outcomes in rhino-orbital cerebral mucormycosis, especially in patients without confirmed CNS involvement, as the mortality was found to be 14% (4 of 29) in the patients with surgery while the patients that received systemic antifungals alone, a mortality of 63% (5 of 8) was observed. In the case of rhino-orbital cerebral mucormycosis with proven CNS involvement, a mortality of 71% (5 of 7 patients) was observed for given systemic antifungals alone, while 57% (8 of 14 patients) mortality was found in patients who had surgery [111]. Another study reported 40 patients having neurological manifestations out of 200 rhino-orbito-cerebral mucormycosis (ROCM) during COVID-19 pandemic. The liposomal amphotericin B and surgical treatment were provided to all the confirmed cases. The neurosurgical intervention with sinus debridement and antifungal treatment was carried out on 7 out of 40 patients with focal lesions in the brain and skull bone. Thus, this study provided different clinical manifestations of ROCM in Indian patients to enable quick diagnosis and invasive surgical approaches may be individualized to lessen the morbidities [112]. Further, another study involving 544 rhino-orbito-cerebral mucormycosis patients including 410 diabetes mellitus patients, it was found, 25 patients were only alive who used only antifungal drug treatment while 428 patients were alive when antifungal drugs were combined with surgical intervention. Thus, surgical debridement is very important along with antifungal treatment to save the life of COVID-19 associated rhino-orbito-cerebral mucormycosis patients [113].

Sen et al. [114] reported studies of 2826 Indian patients affected with COVID-19-associated rhino-orbital-cerebral mucormycosis (ROCM) from January 1, 2020, to May 26, 2021. Notably, 51.9 years was the patient's mean age with 71 % male dominance. Further, 87% patients had corticosteroid treatment and 78 % had Diabetes mellitus. The onset of symptoms of ROCM was observed in 56 % patients within 14 days after COVID-19 diagnosis, while 44% patients had a delayed onset of ROCM beyond 14 days. Further, 72% of patients had involvement of the orbit. The treatment included intravenous amphotericin B in 73 % patients. Further, 56% patients received functional endoscopic sinus surgery (FESS)/paranasal sinus (PNS) debridement, while 15% of patients received orbital exenteration and 17% patients had both FESS/PNS debridement and orbital exenteration. The mortality rate was found to be 14%. The common influencing factor for COVID-19-associated ROCM development involved corticosteroids and diabetes. The early diagnosis, early treatment with amphotericin B, aggressive surgical debridement of the PNS, and orbital exenteration wherever needed were important for the successful management of ROCM [114]. Rao et al. [115] suggested the combined medical and surgical treatment had a lesser recurrence, lower mortality and better results based on studies of 180 patients suspected or confirmed with Rhino-orbital-cerebral mucormycosis or undergone surgery and/or medical treatment or both. Notably, 77.8% patients had post-COVID status and diabetes mellitus was a common risk factor. Interestingly, liposomal Amphotericin B was an efficient antifungal with controllable side effects. Further, 24% of patients were treated with only medical treatment, while 76% of patients had experienced endoscopic or open surgery. A significantly reduced 16.1% mortality and 40% recurrence were observed among 138 operated patients. Further, the radical debridement showed minimal recurrence rates [115]. A study involved 56 patients having COVID-19 associated mucormycosis (CAM), uncontrolled diabetes and steroid treatment. It was found that 43 patients had nasal endoscopic debridement, while 14 patients had maxillectomy. Further, 5 patients needed a temporalis flap and 3 patients needed orbital exenteration. All the patients were treated with lyophilized amphotericin B (deoxycholate) along with surgical debridement and the mortality was found to be 26.31% as a result of early diagnosis, medical treatment and surgical management [116]. Another study involved 287 mucormycosis patients, including 187 patients related to CAM. It was found 71.1% (204/287)) patients had both medical and surgical management. Further, uncontrolled diabetes was found to be most common factor in the CAM patient [117]. Joshi et al. [118] studied 25 COVID-19 hospitalized patients with rhino-orbital-cerebral mucormycosis (ROCM) confirmed by fungal culture. Notably, 22 patients had diabetes and two patients had HIV infection. All the patients were treated with IV amphotericin B in the ICU

and 10 patients had surgical débridement with orbital exenteration; however, 14 patients died [118].

7. Conclusions

Notably, mucormycosis was occurring in both active COVID-19 and post-COVID-19 patients. Most of the mucormycosis patients had COVID-19 treatment with steroids and had a history of diabetes and hypertension. Notably, low immunity and immunocompromised conditions make the environment suitable for mucormycosis.

Many options have been used for the treatment of COVID-19 and post-COVID-19 associated mucormycosis. The first line of therapy includes liposomal amphotericin B, amphotericin B lipid complex and amphotericin B deoxycholate. Further, rescue therapy in the form of posaconazole, deferasirox, adjunctive cytokine therapy, and hyperbaric oxygen [119] could be given when this ailment is not responding to preferred first-line treatment; however, these require additional investigations. Additionally, surgical debridement of mucormycosis was also required to optimize the cure rate.

This review also includes the increased role of iron and zinc in COVID-19 associated mucormycosis (CAM), mechanism of COVID-19 associated mucormycosis (CAM), its clinical trials, therapeutics of COVID-19 associated mucormycosis (CAM), different types of COVID-19 associated mucormycosis (CAM) patients including those having pulmonary mucormycosis, rhino-cerebral mucormycosis, cutaneous mucormycosis, rhino-orbital mucormycosis, gastrointestinal mucormycosis and sino-orbital mucormycosis and their therapeutics; mucormycosis in COVID-19 and post-COVID-19 patients with metabolic disorders, and surgical management of mucormycosis highlighting the potential therapeutic targets for timely intervention and adjunct therapy. This review will enhance the therapeutic strategies and improve the quality-of-life outcomes in CAM patients.

8. Knowledge gaps

Despite the studies about COVID-19 associated mucormycosis and their therapeutics, the knowledge gap remains, which includes.

- detection of early biomarkers for COVID-19 associated mucormycosis remains understudied;
- lack of extensive clinical trials for combination therapy of LAmB with posaconazole or isavuconazole and echinocandin in COVID-19 associated mucormycosis;
- molecular level multi-Omics comparison between Covid-19 associated mucormycosis isolates and non-Covid-19 associated mucormycosis isolates were understudied.

9. Future research directions

The early detection of COVID-19 associated mucormycosis and post-COVID-19 associated mucormycosis determines the patient's outcome [71]. Notably, the early diagnosis of post-COVID-19 associated mucormycosis can be achieved by follow-up of the COVID-19 patients, who had received corticosteroids during their COVID-19 treatment [68]. Early detection and treatment of the COVID-19 associated mucormycosis and post-COVID-19 associated mucormycosis may reduce the high mortality rate and provide better management of the mucormycosis [68,71,120].

Multi-Omics studies at genomic, transcriptomic, and proteomic levels should be undertaken that may reveal the pathogenesis of mucormycosis in Covid-19 associated mucormycosis and non-Covid-19 associated mucormycosis.

In order to reduce the mucormycosis mortality rate, combination therapy of LAmB with posaconazole or isavuconazole and echinocandin needs to be extensively studied in a clinical trial in future.

Notably, a clean, hygienic and healthy environment may help COVID-19 patients to avoid the infection by mucormycosis. Further, the hygienic condition needs to be maintained for months after recovery from COVID-19 infections until the immune system returns to its normal condition.

CRediT authorship contribution statement

Bhaswati Chatterjee: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Suman S. Thakur:** Writing – original draft, Methodology, Formal analysis, Conceptualization.

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References

[1] World Health Organization. COVID-19 Deaths Dashboard. WHO. https://data.who.int/dashboards/covid19/deaths?n=o (accessed December 4, 2025).
[2] B. Chatterjee, S.S. Thakur, ACE2 as potential therapeutic target for pandemic COVID-19, RSC Adv. 10 (65) (2020) 39808–39813, https://doi.org/10.1039/d0ra08228g.
[3] S.S. Thakur, Proteomics and its application in pandemic diseases, J. Proteome Res. 19 (11) (2020) 4215–4218, https://doi.org/10.1021/acs.jproteome.0c00824.
[4] B. Hanley, K.N. Naresh, C. Roufosse, et al., Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study, Lancet Microbe 1 (6) (2020) e245–e253, https://doi.org/10.1016/S2666-5247(20)30115-4.
[5] G. Song, G. Liang, W. Liu, Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China, Mycopathologia 185 (4) (2020) 599–606, https://doi.org/10.1007/s11046-020-00462-9.
[6] A.S. Ibrahim, Host-iron assimilation: pathogenesis and novel therapies of mucormycosis, Mycoses 57 (Suppl 3) (2014) 13–17, https://doi.org/10.1111/myc.12232.
[7] D. Wilson, An evolutionary perspective on zinc uptake by human fungal pathogens, Metallomics 7 (6) (2015) 979–985, https://doi.org/10.1039/c4mt00331d.
[8] T. Tabassum, Y. Araf, A.T. Moin, T.I. Rahaman, M.J. Hosen, COVID-19-associated mucormycosis: possible role of free iron uptake and immunosuppression, Mol. Biol. Rep. 49 (1) (2022) 747–754, https://doi.org/10.1007/s11033-021-06862-4.
[9] S.M. Rudramurthy, M. Hoenigl, J.F. Meis, O.A. Cornely, V. Muthu, J.P. Gangneux, J. Perfect, A. Chakrabarti, ECMM and ISHAM. ECMM/ISHAM recommendations for clinical management of COVID-19-associated mucormycosis in low- and middle-income countries, Mycoses 64 (9) (2021) 1028–1037, https://doi.org/10.1111/myc.13335.
[10] World Health Organization. What can we do to keep safe from mucormycosis? WHO SEARO. https://www.who.int/southeastasia/outbreaks-and-emergencies/covid-19/What-can-we-do-to-keep-safe/mucormycosis (accessed December 4, 2025).
[11] A.K. Johnson, Z. Ghazarian, K.D. Cendrowski, J.G. Persichino, Pulmonary aspergillosis and mucormycosis in a patient with COVID-19, Med Mycol Case Rep 32 (2021) 64–67, https://doi.org/10.1016/j.mmcr.2021.03.006.
[12] Y. Benhadid-Brahmi, S. Hamane, B. Soyer, A. Mebazaa, A. Alanio, B. Chousterman, S. Bretagne, S. Dellière, COVID-19-associated mixed mold infection: a case report of aspergillosis and mucormycosis and a literature review, J. Mycol. Med. 32 (1) (2022) 101231, https://doi.org/10.1016/j.mycmed.2021.101231.
[13] D. Garg, V. Muthu, I.S. Sehgal, et al., Coronavirus disease (COVID-19) associated mucormycosis (CAM): case report and systematic review of literature, Mycopathologia 186 (2) (2021) 289–298, https://doi.org/10.1007/s11046-021-00528-2.
[14] P. Tabarsi, N. Khalili, M. Pourabdollah, S. Sharifynia, A. Safavi Naeini, J. Ghorbani, A. Mohamadnia, Z. Abtahian, E. Askari, Case report: COVID-19-associated rhinosinusitis mucormycosis caused by Rhizopus arrhizus: a rare but potentially fatal infection occurring after treatment with corticosteroids, Am. J. Trop. Med. Hyg. 105 (2) (2021) 449–453, https://doi.org/10.4269/ajtmh.21-0359.
[15] A. Khatri, K.M. Chang, I. Berlinrut, F. Wallach, Mucormycosis after coronavirus disease 2019 infection in a heart transplant recipient: case report and review of literature, J. Mycol. Med. 31 (2) (2021) 101125, https://doi.org/10.1016/j.mycmed.2021.101125.
[16] A. Maini, G. Tomar, D. Khanna, Y. Kini, H. Mehta, V. Bhagyasree, Sino-orbital mucormycosis in a COVID-19 patient: a case report, Int. J. Surg. Case Rep. 82 (2021) 105957, https://doi.org/10.1016/j.ijscr.2021.105957.
[17] C. Zurl, M. Hoenigl, E. Schulz, et al., Autopsy-proven pulmonary mucormycosis due to Rhizopus microsporus in a critically ill COVID-19 patient with underlying hematological malignancy, J. Fungi 7 (2) (2021) 88, https://doi.org/10.3390/jof7020088.
[18] A. Moorthy, R. Gaikwad, S. Krishna, et al., SARS-CoV-2, uncontrolled diabetes and corticosteroids—an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis, J. Maxillofac. Oral Surg. 20 (2021) 1–8, https://doi.org/10.1007/s12663-021-01532-1.
[19] A. Werthman-Ehrenreich, Mucormycosis with orbital compartment syndrome in a patient with COVID-19, Am. J. Emerg. Med. 42 (2021) 264.e5–264.e8, https://doi.org/10.1016/j.ajem.2020.09.032.
[20] World Health Organization, Mucormycosis: incidence in India. WHO India. https://www.who.int/india/home/emergencies/coronavirus-disease-(covid-19)/mucormycosis#:~:text=The%20incidence%20rate%20of%20mucormycosis,the%20prevalence%20in%20developed%20countries accessed December 4, 2025).
[21] A.A. Balushi, A.A. Ajmi, Q.A. Sinani, et al., COVID-19-associated mucormycosis: an opportunistic fungal infection. A case series and review, Int. J. Infect. Dis. 121 (2022) 203–210, https://doi.org/10.1016/j.ijid.2022.05.005.
[22] A. Kasatwar, R. Shukla, N. Rathod, et al., Insights from surgically treated post-COVID acute invasive fungal rhino-orbital sinusitis in Chandrapur study (SPAROS): a population-based study of coronavirus associated mucormycosis (CAM) characteristics in India, IJID Reg. 5 (2022) 21–29, https://doi.org/10.1016/j.ijregi.2022.08.005.
[23] H. Prakash, A. Chakrabarti, Global epidemiology of mucormycosis, J. Fungi 5 (1) (2019) 26, https://doi.org/10.3390/jof5010026.
[24] O.A. Cornely, A. Alastruey-Izquierdo, D. Arenz, et al., Global guideline for the diagnosis and management of mucormycosis: an initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium, Lancet Infect. Dis. 19 (12) (2019) e405–e421, https://doi.org/10.1016/S1473-3099(19)30312-3.
[25] World Health Organization. Mucormycosis in India. WHO India. https://www.who.int/india/home/emergencies/coronavirus-disease-(covid-19)/mucormycosis (accessed December 4, 2025).

[26] P. Dam, M.H. Cardoso, S. Mandal, et al., Surge of mucormycosis during the COVID-19 pandemic, Trav. Med. Infect. Dis. 52 (2023) 102557, https://doi.org/10.1016/j.tmaid.2023.102557.
[27] I.C.N. Rocha, M.M. Hasan, S. Goyal, et al., COVID-19 and mucormycosis syndemic: double health threat to a collapsing healthcare system in India, Trop. Med. Int. Health 26 (9) (2021) 1016–1018, https://doi.org/10.1111/tmi.13641.
[28] A.K. Singh, R. Singh, S.R. Joshi, A. Misra, Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India, Diabetes Metabol. Syndr. 15 (4) (2021) 102146, https://doi.org/10.1016/j.dsx.2021.05.019.
[29] A.S. Fathima, V.L. Mounika, V.U. Kumar, et al., Mucormycosis: a triple burden in patients with diabetes during COVID-19 pandemic, Health Sci. Rev. 1 (2021) 100005, https://doi.org/10.1016/j.hsr.2021.100005.
[30] A.S. Ibrahim, B. Spellberg, J. Edwards Jr., Iron acquisition: a novel perspective on mucormycosis pathogenesis and treatment, Curr. Opin. Infect. Dis. 21 (6) (2008 Dec) 620–625, https://doi.org/10.1097/QCO.0b013e3283165fd1.
[31] A.S. Ibrahim, J.E. Edwards, S.G. Filler, Zygomycosis, in: W.E. Dismukes, P.G. Pappas, J.D. Sobel (Eds.), Clinical Mycology, Oxford University Press, New York, 2003, pp. 241–251.
[32] I. Dp, M.I.K. Yadhav, G.S. Chetana, Is serum ferritin an early marker for COVID-19-associated mucormycosis? Cureus 15 (3) (2023) e36734 https://doi.org/10.7759/cureus.36734.
[33] S. Bhadania, N. Bhalodiya, Y. Sethi, et al., Hyperferritinemia and the extent of mucormycosis in COVID-19 patients, Cureus 13 (12) (2021) e20569, https://doi.org/10.7759/cureus.20569.
[34] N.N. Shah, Z. Khan, H. Ahad, et al., Mucormycosis: an added burden to COVID-19 patients—an in-depth systematic review, J. Infect. Public Health 15 (11) (2022) 1299–1314, https://doi.org/10.1016/j.jiph.2022.10.011.
[35] I. Theurl, E. Aigner, M. Theurl, et al., Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications, Blood 113 (21) (2009) 5277–5286, https://doi.org/10.1182/blood-2008-12-195651.
[36] K.F. Kernan, J.A. Carcillo, Hyperferritinemia and inflammation, Int. Immunol. 29 (9) (2017) 401–409, https://doi.org/10.1093/intimm/dxx031.
[37] E. Nemeth, S. Rivera, V. Gabayan, et al., IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin, J. Clin. Investig. 113 (9) (2004) 1271–1276, https://doi.org/10.1172/JCI20945.
[38] G. Comentale, R. Manzo, E. Pilato, SARS-CoV-2 interference in HEME production: is it the time for an early predictive biomarker? J. Mol. Med. (Berl.) 98 (8) (2020) 1053–1054, https://doi.org/10.1007/s00109-020-01945-4.
[39] A. Russo, E. Tellone, D. Barreca, S. Ficarra, G. Laganà, Implication of COVID-19 on erythrocytes functionality: red blood cell biochemical implications and morpho-functional aspects, Int. J. Mol. Sci. 23 (4) (2022) 2171, https://doi.org/10.3390/ijms23042171.
[40] E. Suriawinata, K.J. Mehta, Iron and iron-related proteins in COVID-19, Clin. Exp. Med. 23 (4) (2023) 969–991, https://doi.org/10.1007/s10238-022-00851-y.
[41] S. Imashuku, Clinical evaluation of hyperferritinemia with or without iron overload, J. Lab. Precis. Med. 9 (2024) 16, 10.21037/.
[42] B. Nongtdu, A.A. Ruram, I. Tiewsoh, S.P. Sundaram, P. Boruah, Serum ferritin as a prognostic marker in COVID-19, J. Appl. Sci. Clin. Pract. 5 (1) (2024) 52–56, https://doi.org/10.4103/jascp.jascp_1_24.
[43] F. Deng, L. Zhang, L. Lyu, et al., Increased levels of ferritin on admission predict intensive care unit mortality in patients with COVID-19, Med. Clin. 156 (7) (2021) 324–331, https://doi.org/10.1016/j.medcli.2020.11.030.
[44] C.C. Staats, L. Kmetzsch, A. Schrank, M.H. Vainstein, Fungal zinc metabolism and its connections to virulence, Front. Cell. Infect. Microbiol. 3 (2013) 65, https://doi.org/10.3389/fcimb.2013.00065.
[45] J.W. Foster, S.A. Waksman, The specific effect of zinc and other heavy metals on the growth and nutrition of Rhizopus, J. Bacteriol. 37 (6) (1939) 599–617, https://doi.org/10.1128/jb.37.6.599-617.1939.
[46] V. Muthu, M. Kumar, R.A. Paul, et al., Is there an association between zinc and COVID-19-associated mucormycosis? Results of an experimental and clinical study, Mycoses 64 (10) (2021) 1291–1297, https://doi.org/10.1111/myc.13365.
[47] D. Pasero, S. Sanna, C. Liperi, et al., A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis, Infection 49 (5) (2021) 1055–1060, https://doi.org/10.1007/s15010-020-01561-x.
[48] V.J. Costela-Ruiz, R. Illescas-Montes, J.M. Puerta-Puerta, C. Ruiz, L. Melguizo-Rodríguez, SARS-CoV-2 infection: the role of cytokines in COVID-19 disease, Cytokine Growth Factor Rev. 54 (2020) 62–75, https://doi.org/10.1016/j.cytogfr.2020.06.001.
[49] J. Kim, J.H. Nam, Insight into the relationship between obesity-induced low-level chronic inflammation and COVID-19 infection, Int. J. Obes. 44 (7) (2020) 1541–1542, https://doi.org/10.1038/s41366-020-0602-y.
[50] M.A. Atkinson, A.C. Powers, Distinguishing the real from the hyperglycaemia: does COVID-19 induce diabetes? Lancet Diabetes Endocrinol. 9 (6) (2021) 328–329, https://doi.org/10.1016/S2213-8587(21)00087-5.
[51] L. Potenza, D. Vallerini, P. Barozzi, et al., Mucorales-specific T cells emerge in the course of invasive mucormycosis and may be used as a surrogate diagnostic marker in high-risk patients, Blood 118 (20) (2011) 5416–5419, https://doi.org/10.1182/blood-2011-07-366526.
[52] J. Liu, S. Li, J. Liu, et al., Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients, EBioMedicine 55 (2020) 102763, https://doi.org/10.1016/j.ebiom.2020.102763.
[53] L. Özbek, U. Topçu, M. Manay, et al., COVID-19-associated mucormycosis: a systematic review and meta-analysis of 958 cases, Clin. Microbiol. Infect. 29 (6) (2023) 722–731, https://doi.org/10.1016/j.cmi.2023.03.008.
[54] S. Hussain, H. Baxi, A. Riad, et al., COVID-19-associated mucormycosis (CAM): an updated evidence mapping, Int. J. Environ. Res. Publ. Health 18 (19) (2021) 10340, https://doi.org/10.3390/ijerph181910340.
[55] V.U.S. Rao, G. Arakeri, G. Madikeri, et al., COVID-19 associated mucormycosis (CAM) in India: a formidable challenge, Br. J. Oral Maxillofac. Surg. 59 (9) (2021) 1095–1098, 10.101.
[56] R. Gupta, J. Kesavadev, G. Krishnan, S. Agarwal, B. Saboo, M. Shah, A. Mittal, S. Durani, A. Luthra, A. Singhal, M. Rasheed, G.V.S. Rao, V. Tripathi, A. Jha, A. Ghosh, V. Mohan, A.K. Singh, S. Phatak, J. Panicker, S.K. Bhadada, S. Joshi, R. Pal, A. Mithal, N. Vikram, A. Misra, COVID-19 associated mucormycosis: a descriptive multisite study from India, Diabetes Metabol. Syndr. 15 (6) (2021) 102322, https://doi.org/10.1016/j.dsx.2021.102322.
[57] A. Ramaswami, A.K. Sahu, A. Kumar, S. Suresh, A. Nair, D. Gupta, R. Chouhan, R. Bhat, R. Mathew, J.A. Majeed, P. Aggarwal, J. Nayer, M. Ekka, A. Thakar, G. Singh, I. Xess, N. Wig, COVID-19-associated mucormycosis presenting to the emergency department—an observational study of 70 patients, QJM 114 (7) (2021) 464–470, https://doi.org/10.1093/qjmed/hcab190.
[58] R. Meher, V. Wadhwa, V. Kumar, D.S. Phanbuh, R. Sharma, I. Singh, P.K. Rathore, R. Goel, R. Arora, S. Garg, S. Kumar, J. Kumar, M. Agarwal, M. Singh, N. Khurana, T. Sagar, V. Manchanda, S. Saxena, COVID-associated mucormycosis: a preliminary study from a dedicated COVID hospital in Delhi, Am. J. Otolaryngol. 43 (1) (2022) 103220, https://doi.org/10.1016/j.amjoto.2021.103220.
[59] M. Toppo, D. Gour, R.S. Lodha, M. Kamble, S. Keerthana, A case-control study on mucormycosis in tertiary care hospital, Bhopal, Indian J. Community Med. 47 (3) (2022) 396–399, https://doi.org/10.4103/ijcm.ijcm_1320_21.
[60] N. Singla, N. Sharma, N. Sharma, A. Behera, M. Bhatia, Clinical profile of patients admitted with mucormycosis during the COVID-19 pandemic in medicine emergency of a tertiary care hospital in North India, Cureus 14 (9) (2022) e29219, https://doi.org/10.7759/cureus.29219.
[61] A. Irfan, A.H. Kamran, M. Ammar, S.U. Rahman, Frequency and survival of COVID-associated mucormycosis patients at tertiary care hospitals in Pakistan: a retrospective observational study, Health Sci. Rep. 6 (2) (2023) e1083, https://doi.org/10.1002/hsr2.1083.
[62] V. Muthu, R.R. Gogineni, R. Agarwal, K.T. Prasad, I.S. Sehgal, S. Dhooria, A.N. Aggarwal, S.M. Rudramurthy, H. Singh, M. Garg, A. Chakrabarti, Treatment of pulmonary mucormycosis with adjunctive nebulized amphotericin B (MUCONAB trial): results of an open-label randomized controlled trial, Mycoses 66 (8) (2023) 688–696, https://doi.org/10.1111/myc.13591.
[63] Z. Shaikh, A. Mishra, S. Chadaram, C. Preetam, R. Biswas, A. Adhikari, A. Alagappan, P.K. Parida, P. Pradhan, D.K. Samal, S. Mahakud, V. Hallur, A. Nayak, K. K. Das, S. Chakraborty, P. Sharma, A.K. Veetil, V. Karakkandy, Y. Mittal, K.S. Chithambaram, A. Swarup, S. Chenniappan, A. Shah, To evaluate the efficacy of

topical anti-fungal therapy in postoperative cases of COVID-associated mucormycosis (CAM): a single-blinded randomized control trial, Am. J. Otolaryngol. 44 (2) (2023) 103702, https://doi.org/10.1016/j.amjoto.2022.103702.
[64] J.-P. Gangneux, E. Dannaoui, A. Fekkar, C.-E. Luyt, F. Botterel, N. De Prost, et al., Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study, Lancet Respir. Med. 10 (2) (2022) 180–190, https://doi.org/10.1016/S2213-2600(21)00442-2.
[65] S. Farghly Youssif, M.M. Abdelrady, A.A. Thabet, et al., COVID-19 associated mucormycosis in Assiut University Hospitals: a multidisciplinary dilemma, Sci. Rep. 12 (2022) 10494, https://doi.org/10.1038/s41598-022-13443-3.
[66] A. Abdoli, S. Falahi, A. Kenarkoohi, COVID-19-associated opportunistic infections: a snapshot on the current reports, Clin. Exp. Med. 22 (3) (2022) 327–346, https://doi.org/10.1007/s10238-021-00751-7.
[67] D. Ghalwash, A. Abou-Bakr, R.R. Hussein, A.A. El-Gawish, Comorbidities and final outcome of post-COVID-19 associated oral mucormycosis patients: a cross-sectional study, Egypt J. Otolaryngol. 40 (2024) 51, https://doi.org/10.1186/s43163-024-00614-4.
[68] N. Sundaram, T. Bhende, R. Yashwant, S. Jadhav, A. Jain, Mucormycosis in COVID-19 patients, Indian J. Ophthalmol. 69 (12) (2021) 3728–3733, https://doi.org/10.4103/ijo.IJO_1316_21.
[69] A. Taneja, B. Singh, S. Kaura, D.S. Chawla, G. Singh, M. Kaur, Mucormycosis and COVID-19- black threat of the pandemic, Int. J. Res. Med. Sci. 11 (7) (2023) 2513–2516, https://doi.org/10.18203/2320-6012.ijrms20232092.
[70] R. Soman, S. Chakraborty, G. Joe, Posaconazole or isavuconazole as sole or predominant antifungal therapy for COVID-19-associated mucormycosis: a retrospective observational case series, Int. J. Infect. Dis. 120 (2022) 177–178, https://doi.org/10.1016/j.ijid.2022.04.009.
[71] V. Muthu, R. Agarwal, A. Patel, S. Kathirvel, O.C. Abraham, A.N. Aggarwal, A. Bal, A.S. Bhalla, P.N. Chhajed, D. Chaudhry, M. Garg, R. Guleria, R.G. Krishnan, A. Kumar, U. Maheshwari, R. Mehta, A. Mohan, A. Nath, D. Patel, S.M. Rudramurthy, P. Saxena, N. Sethuraman, T. Singhal, R. Soman, B. Thangakunam, G. M. Varghese, A. Chakrabarti, Definition, diagnosis, and management of COVID-19-associated pulmonary mucormycosis: delphi consensus statement from the fungal infection study forum and academy of pulmonary sciences, India, Lancet Infect. Dis. 22 (9) (2022) e240–e253, https://doi.org/10.1016/S1473-3099(22)00124-4.
[72] M. Mukherjee, A.K. Verma, T. Bandyopadhyay, V.V.D.P. Kumar, S.S. Reddy, Optimization of oral posaconazole step-down therapy in management of rhino-orbital-cerebral mucormycosis (ROCM): outcome of an institutional protocol, Indian J. Otolaryngol. Head Neck Surg. 75 (4) (2023) 1–7, https://doi.org/10.1007/s12070-023-03889-w.
[73] J.M. Aranjani, A. Manuel, H.I. Abdul Razack, S.T. Mathew, COVID-19-associated mucormycosis: evidence-based critical review of an emerging infection burden during the pandemic's second wave in India, PLoS Neglected Trop. Dis. 15 (11) (2021) e0009921, https://doi.org/10.1371/journal.pntd.0009921.
[74] S.G. Honavar, Code Mucor: guidelines for the diagnosis, staging and management of rhino-orbitocerebral mucormycosis in the setting of COVID-19, Indian J. Ophthalmol. 69 (6) (2021) 1361–1365, https://doi.org/10.4103/ijo.IJO_1165_21.
[75] A. Keshri, A. Mathialagan, A. Aishwarya, Bhuskute G. Ravisankar, V. Kanaujia, A.K. Singh, R.K. Singh, R.K. Dhiman, R. Agarwal, Is mucormycosis the end? A comprehensive management of orbit in COVID-associated rhino-orbital-cerebral mucormycosis: preserving the salvageable, Eur. Arch. Otorhinolaryngol. 280 (2) (2023) 819–827, https://doi.org/10.1007/s00405-022-07620-3.
[76] R.P. Maurya, Indications for orbital exenteration in COVID-19 associated rhino-orbito-cerebral mucormycosis, IP Int. J. Ocul. Oncol. Oculoplasty 7 (2) (2021) 105–108, https://doi.org/10.18231/j.ijooo.2021.023.
[77] L.C. García-Carnero, H.M. Mora-Montes, Mucormycosis and COVID-19-associated mucormycosis: insights of a deadly but neglected mycosis, J. Fungi 8 (2022) 445, https://doi.org/10.3390/jof8050445.
[78] H. Dandu, N. Kumar, N. Kumar, H.S. Malhotra, V. Prabhu, V.R. Bharti, P. Gupta, G. Yadav, V. Verma, Utility of itraconazole in combination with liposomal amphotericin B in *Rhizopus oryzae* associated mucormycosis—an exploratory study, Mycopathologia 189 (4) (2024) 54, https://doi.org/10.1007/s11046-024-00859-w.
[79] A.B. Rajendra Santosh, K. Muddana, S.R. Bakki, Fungal infections of oral cavity: diagnosis, management, and association with COVID-19, SN Compr. Clin. Med. 3 (6) (2021) 1373–1384, https://doi.org/10.1007/s42399-021-00873-9.
[80] K. Bhatt, A. Agolli, M.H. Patel, R. Garimella, M. Devi, E. Garcia, H. Amin, C. Domingue, R. Guerra Del Castillo, M. Sanchez-Gonzalez, High mortality co-infections of COVID-19 patients: mucormycosis and other fungal infections, Discoveries 9 (1) (2021) e126, https://doi.org/10.15190/d.2021.5.
[81] J.M. Aranjani, A. Manuel, H.I. Abdul Razack, S.T. Mathew, COVID-19-associated mucormycosis: evidence-based critical review of an emerging infection burden during the pandemic's second wave in India, PLoS Neglected Trop. Dis. 15 (11) (2021 Nov 18) e0009921, https://doi.org/10.1371/journal.pntd.0009921.
[82] N.R. Stone, T. Bicanic, R. Salim, W. Hope, Liposomal amphotericin B (AmBisome®): a review of the pharmacokinetics, pharmacodynamics, clinical experience and future directions, Drugs 76 (4) (2016) 485–500, https://doi.org/10.1007/s40265-016-0538-7.
[83] J. Adler-Moore, AmBisome targeting to fungal infections, Bone Marrow Transplant. 14 (Suppl 5) (1994) S3–S7.
[84] J.D. Readio, R. Bittman, Equilibrium binding of amphotericin B and its methyl ester and borate complex to sterols, Biochim. Biophys. Acta 685 (2) (1982) 219–224, https://doi.org/10.1016/0005-2736(82)90103-1.
[85] K. Shimizu, M. Osada, K. Takemoto, Y. Yamamoto, T. Asai, N. Oku, Temperature-dependent transfer of amphotericin B from liposomal membrane of AmBisome to fungal cell membrane, J. Contr. Release 141 (2) (2010) 208–215, https://doi.org/10.1016/j.jconrel.2009.09.019.
[86] I. Bekersky, R.M. Fielding, D.E. Dressler, J.W. Lee, D.N. Buell, T.J. Walsh, Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans, Antimicrob. Agents Chemother. 46 (3) (2002) 828–833, https://doi.org/10.1128/AAC.46.3.828-833.2002.
[87] S. Mistro, M. Maciel Ide, R.G. de Menezes, Z.P. Maia, R.T. Schooley, R. Badaró, Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis, Clin. Infect. Dis. 54 (12) (2012) 1774–1777, https://doi.org/10.1093/cid/cis290.
[88] I. Bekersky, G.W. Boswell, R. Hiles, R.M. Fielding, D. Buell, T.J. Walsh, Safety, toxicokinetics and tissue distribution of long-term intravenous liposomal amphotericin B (AmBisome): a 91-day study in rats, Pharm. Res. 17 (12) (2000) 1494–1502, https://doi.org/10.1023/A:1007605024942.
[89] R.L. Wade, P. Chaudhari, J.L. Natoli, R.J. Taylor, B.H. Nathanson, D.L. Horn, Nephrotoxicity and other adverse events among inpatients receiving liposomal amphotericin B or amphotericin B lipid complex, Diagn. Microbiol. Infect. Dis. 76 (3) (2013) 361–367, https://doi.org/10.1016/j.diagmicrobio.2013.04.001.
[90] G.P. Patel, C.W. Crank, J.B. Leikin, An evaluation of hepatotoxicity and nephrotoxicity of liposomal amphotericin B (L-AMB), J. Med. Toxicol. 7 (1) (2011) 12–15, https://doi.org/10.1007/s13181-010-0120-8.
[91] G. Chamilos, M. Luna, R.E. Lewis, R. Chemaly, I. Raad, D.P. Kontoyiannis, Effects of liposomal amphotericin B versus an amphotericin B lipid complex on liver histopathology in patients with hematologic malignancies and invasive fungal infections: a retrospective, nonrandomized autopsy study, Clin. Ther. 29 (9) (2007) 1980–1986, https://doi.org/10.1016/j.clinthera.2007.09.016.
[92] C. Smith, S.C. Lee, Current treatments against mucormycosis and future directions, PLoS Pathog. 18 (10) (2022 Oct 13) e1010858, https://doi.org/10.1371/journal.ppat.1010858.
[93] R. Murthy, A. Bagchi, Y. Gote, S. Desai, Retrobulbar injection of amphotericin B using intravenous cannula for post-COVID-19 rhino-orbital mucormycosis, Indian J. Ophthalmol. 70 (1) (2022) 302–305, https://doi.org/10.4103/ijo.IJO_1511_21.
[94] A. Sharifi, Z. Akbari, M. Shafie'ei, N. Nasiri, M. Sharifi, M. Shafiei, A. Zand, Retrobulbar injection of amphotericin B in patients with COVID-19 associated orbital mucormycosis: a systematic review, Ophthalmic Plast. Reconstr. Surg. 38 (5) (2022) 425–432, https://doi.org/10.1097/IOP.0000000000002256.
[95] L.B. Ramamurthy, R. Bhandari, S. Kanakpur, P. Thejaswini, Outcome of transcutaneous retrobulbar injection of liposomal amphotericin B in post-COVID-19 rhino-orbito-cerebral mucormycosis: our experience, Indian J. Ophthalmol. 70 (3) (2022) 1019–1024, https://doi.org/10.4103/ijo.IJO_2356_21.
[96] J. Shakrawal, V. Sharma, A. Goyal, D. Kumar, S. Meena, S. Tiwari, V. Jain, P. Elhence, K. Soni, B. Choudhury, K. Bhatnagar, M.K. Garg, S. Misra, Outcomes of transcutaneous retrobulbar amphotericin B (TRAMB) as an adjuvant therapy for rhino-orbital-cerebral mucormycosis (ROCM) following COVID-19, Int. Ophthalmol. 43 (6) (2023) 1919–1926, https://doi.org/10.1007/s10792-022-02591-0.
[97] A. Veisi, A. Bagheri, M. Eshaghi, M.H.R. Rikhtehgar, A. RezaeiKanavi, R. Farjad, Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: a case report, Eur. J. Ophthalmol. 32 (4) (2022) NP11–NP16, https://doi.org/10.1177/11206721211009450.

[98] S. Acharya, S.K. Behera, S. Purohit, A. Sahu, B.B. Panda, S. Behera, COVID-19-associated rhino-orbital mucormycosis in a tertiary health care center in Odisha, India, Cureus 15 (8) (2023) e43811, https://doi.org/10.7759/cureus.43811.
[99] M. Sen, S. Lahane, T.P. Lahane, R. Parekh, S.G. Honavar, Mucor in a viral land: a tale of two pathogens, Indian J. Ophthalmol. 69 (2) (2021) 244–252, https://doi.org/10.4103/ijo.IJO_3774_20.
[100] M. Ellsworth, L. Ostrosky-Zeichner, Isavuconazole: mechanism of action, clinical efficacy, and resistance, J. Fungi 6 (4) (2020) 324, https://doi.org/10.3390/jof6040324.
[101] J. Livermore, W. Hope, Evaluation of the pharmacokinetics and clinical utility of isavuconazole for treatment of invasive fungal infections, Expert Opin. Drug Metab. Toxicol. 8 (6) (2012) 759–765, https://doi.org/10.1517/17425255.2012.683859.
[102] D.A. Placik, W.L. Taylor, N.M. Wnuk, Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia, Radiol. Case Rep. 15 (11) (2020) 2378–2381, https://doi.org/10.1016/j.radcr.2020.09.026.
[103] K. Alekseyev, L. Didenko, B. Chaudhry, Rhinocerebral mucormycosis and COVID-19 pneumonia, J. Med. Cases 12 (3) (2021) 85–89, https://doi.org/10.14740/jmc3637.
[104] Z.K. Mekonnen, D.C. Ashraf, T. Jankowski, S.R. Grob, M.R. Vagefi, R.C. Kersten, J.P. Simko, B.J. Winn, Acute invasive rhino-orbital mucormycosis in a patient with COVID-19-associated acute respiratory distress syndrome, Ophthalmic Plast. Reconstr. Surg. 37 (2) (2021) e40–e80, https://doi.org/10.1097/IOP.0000000000001889.
[105] S. Waizel-Haiat, J.A. Guerrero-Paz, L. Sanchez-Hurtado, S. Calleja-Alarcon, L. Romero-Gutierrez, A case of fatal rhino-orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID-19, Cureus 13 (2) (2021) e13163, https://doi.org/10.7759/cureus.13163.
[106] E.S.D. Monte Junior, M.E.L.D. Santos, I.B. Ribeiro, G.O. Luz, E.R. Baba, B.S. Hirsch, M.P. Funari, E.G.H. de Moura, Rare and fatal gastrointestinal mucormycosis (zygomycetes) in a COVID-19 patient: a case report, Clin. Endosc. 53 (6) (2020) 746–749, https://doi.org/10.5946/ce.2020.180.
[107] A. Maini, G. Tomar, D. Khanna, Y. Kini, H. Mehta, V. Bhagyasree, Sino-orbital mucormycosis in a COVID-19 patient: a case report, Int. J. Surg. Case Rep. 82 (2021) 105957, https://doi.org/10.1016/j.ijscr.2021.105957.
[108] T.M. John, C.N. Jacob, D.P. Kontoyiannis, When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis, J. Fungi 7 (4) (2021) 298, https://doi.org/10.3390/jof7040298.
[109] S. Sharma, M. Grover, S. Bhargava, et al., Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum, J. Laryngol. Otol. (2021) 1–6, https://doi.org/10.1017/S0022215121000992.
[110] D. Girdhar, E. Manocha, A comprehensive review on the management of COVID-19-associated mucormycosis (CAM): the new basics, BioMed 2 (2022) 181–198, https://doi.org/10.3390/biomed2020017.
[111] M. Hoenigl, D. Seidel, A. Carvalho, S.M. Rudramurthy, A. Arastehfar, J.P. Gangneux, N. Nasir, A. Bonifaz, J. Araiza, N. Klimko, et al., ECMM and ISHAM collaborators, The emergence of COVID-19-associated mucormycosis: a review of cases from 18 countries, Lancet Microbe 3 (7) (2022) e543–e552, https://doi.org/10.1016/S2666-5247(21)00237-8.
[112] A.K. Das, S.K. Mani, S.K. Singh, Surgical management of post-COVID invasive rhino-orbito-cerebral mucormycosis and its outcomes: role of neurosurgeons in a tertiary care center, Surg. Neurol. Int. 13 (2022) 335, https://doi.org/10.25259/SNI_374_2022.
[113] S. Chopra, S. Setiya, P.P. Waknis, L. Kale, S. Tidke, Various treatment modalities in COVID-19 associated facial mucormycosis and the need for its surgical management: a systematic review, J. Maxillofac. Oral Surg. (2023) 1–22, https://doi.org/10.1007/s12663-023-01878-8.
[114] M. Sen, S.G. Honavar, R. Bansal, S. Sengupta, R. Rao, U. Kim, M. Sharma, M. Sachdev, A.K. Grover, A. Surve, et al., Collaborative OPAI-IJO study on mucormycosis in COVID-19 (COSMIC) study group. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India—COSMIC, report 1, Indian J. Ophthalmol. 69 (7) (2021) 1670–1692, https://doi.org/10.4103/ijo.IJO_1565_21.
[115] K.M. Rao, N. Pooja, Management of mucormycosis in post COVID-19 patients and its outcome in a tertiary care center: our experience, Indian J. Otolaryngol. Head Neck Surg. 74 (Suppl 2) (2022) 3344–3351, https://doi.org/10.1007/s12070-022-03197-9.
[116] N.M. Solanki, R.N. Solanki, A.V. Madaliya, R.H. Jasoliya, D.T. Upadhyay, COVID-19-associated mucormycosis: an update of anesthetic management, Ain Shams J. Anaesthesiol. 14 (1) (2022) 16, https://doi.org/10.1186/s42077-022-00216-3.
[117] A. Patel, R. Agarwal, S.M. Rudramurthy, M. Shevkani, I. Xess, R. Sharma, et al., Multicenter epidemiologic study of coronavirus disease–associated mucormycosis, India, Emerg. Infect. Dis. 27 (9) (2021) 2349–2359, https://doi.org/10.3201/eid2709.210934.
[118] A.R. Joshi, M.M. Muthe, S.H. Patankar, A. Athawale, Y. Achhapalia, CT and MRI findings of invasive mucormycosis in the setting of COVID-19: experience from a single center in India, AJR Am. J. Roentgenol. 217 (6) (2021) 1431–1432, https://doi.org/10.2214/AJR.21.26205.
[119] B. Spellberg, A. Ibrahim, Recent advances in the treatment of mucormycosis, Curr. Infect. Dis. Rep. 12 (6) (2010) 423–429, https://doi.org/10.1007/s11908-010-0129-9.
[120] A. Azhar, W.H. Khan, P.A. Khan, K. Alhosaini, M. Owais, A. Ahmad, Mucormycosis and COVID-19 pandemic: clinical and diagnostic approach, J. Infect. Public Health 15 (4) (2022) 466–479, https://doi.org/10.1016/j.jiph.2022.02.007.