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# Agents of mucormycosis outbreak associated with COVID-19

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**Abstract**

Mucormycosis is a life-threatening infection. Mucormycetes causes a wide range of diseases, including pneumonia, rhinosinusitis, internal organ spread, gastrointestinal tract involvement, and skin and soft tissue infection. It infects predominantly with hematological malignancies, transplantation, immunocompromised, and diabetes mellitus patients. The most severe type of the disease is a disseminated disease, which is linked to significant immunosuppression. Currently, this disease is more prevalent in the COVID-19 pandemic because of erroneous steroid use and untreated diabetes. However, there is a scarcity of study and information on the COVID-19 and mucormycosis connection. According to the latest research, mucormycosis cases are rising in developed and developing nations, and only a few therapies are available. The exact burden of mucormycosis is unclear; however, it is likely to be greater than recorded instances due to mucormycosis epidemiological changes. As a result of the delay in identifying this severe illness, appropriate antifungal medications are delayed, resulting in significant morbidity and death. A few drugs are underclinical trials for their efficacy. Other obstacles to treat patients are lack of reliable diagnostic non-invasive tests. This review article draws the attention of its readers and clinicians towards the agents of mucormycosis and discuss the various cases to manage this fungal infection.

## 1. Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) has been related to many opportunistic fungal and bacterial infections (Kubin *et al.*, 2021; Ahmad *et al.*, 2021). Pathogens that are developing or re-emerging, pose a worldwide threat to public health (Gao, 2018). Fungal pathogens Candida and Aspergillosis have been reported to be accountable for co-infection in people with COVID-19 (Paltauf, 2021). Coronaviruses are enveloped RNA viruses that cause respiratory, hepatic, neurological, and gastrointestinal illnesses in humans, other animals, and birds (Liu, 2014; Weiss and Leibowitz, 2011; Khan *et al.*, 2020). Even though, COVID-19 primarily affects the lungs, several clinical consequences have been observed, including cardiac damage, thromboembolic events, arrhythmia, and immunological dysregulation (Giustino *et al.*, 2020; Tay *et al.*, 2020; Diao *et al.*, 2020; Wahab, *et al.*, 2021). Sufferers with acute respiratory distress syndrome (ARDS) given corticosteroids, broad-spectrum antibiotics, and invasive or non-invasive ventilation are more prone to get co-infections. According to a recent report, co-infection is present in 63.64% of COVID-19 mortality (Lv *et al.*, 2020; Wahab, *et al.*, 2021). Mucormycosis, acknowledged as “black fungus,” is a rare but fatal fungal illness found in COVID-19 patients in many Indian states (Singh *et al.*, 2021). Mucormycosis is caused by the mucor mold often found in plants, manure, rotting vegetables, fruits, and soil. These fungi proliferate a vast quantity of spores into the atmosphere. Inhalation is a common way for humans to come into contact with these fungi (Hirabayashi *et al.*, 2019). It affects the sinuses, brain and lungs and may be deadly for immunocompromised or have diabetes or, cancer or people living with HIV/AIDS. Rhino-orbital mucormycosis is becoming more usual in persons with COVID-19. These instances are very prevalent in India currently. Diabetes mellitus (DM) is linked to severe COVID-19 infection and mucormycosis (Singh *et al.*, 2021). Immunocompromised and poorly managed diabetic patients are typically affected, with severe morbidity and death (John *et al.*, 2021). Mucormycosis has also been found in the pulmonary and gastrointestinal tract (Do Monte *et al.*, 2020; Garg *et al.*, 2021).

Until today, few studies have aimed to look for superinfections by fungus, bacteria, or other viruses in SARS-CoV-2 cases (Agrifoglio *et al.*, 2020; Garcia-Vidal *et al.*, 2020). Patients with a mucormycosis (MCR) - like illness, such as rhino-orbital illness and a positive nasal cavity culture, were judged as having “probable” MCR. Individuals with cavitary pneumonia and SARS-CoV-2 infection with mucorales isolated from their respiratory secretions had “putative” MCR. If

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there were signs of infection on arrival, mucormycosis was classed as “concurrent” and “sequential”, if a diagnosis was made 72 hours after the COVID-19 diagnosis (John *et al.*, 2021; Bakshi and Kalidoss, 2021). However, research and information concerning the link between COVID-19 and mucormycosis are limited. Early identification and recognition of illness patterns are critical in the treatment of mucormycosis. Patients in low and medium income countries suffered by a lack of access to modern therapies. In the current epidemic situation, it is necessary to sensitize the clinicians as the risk of fatal infection rises. Hence, we reviewed literature reporting mucormycosis in patients to provide updated information.

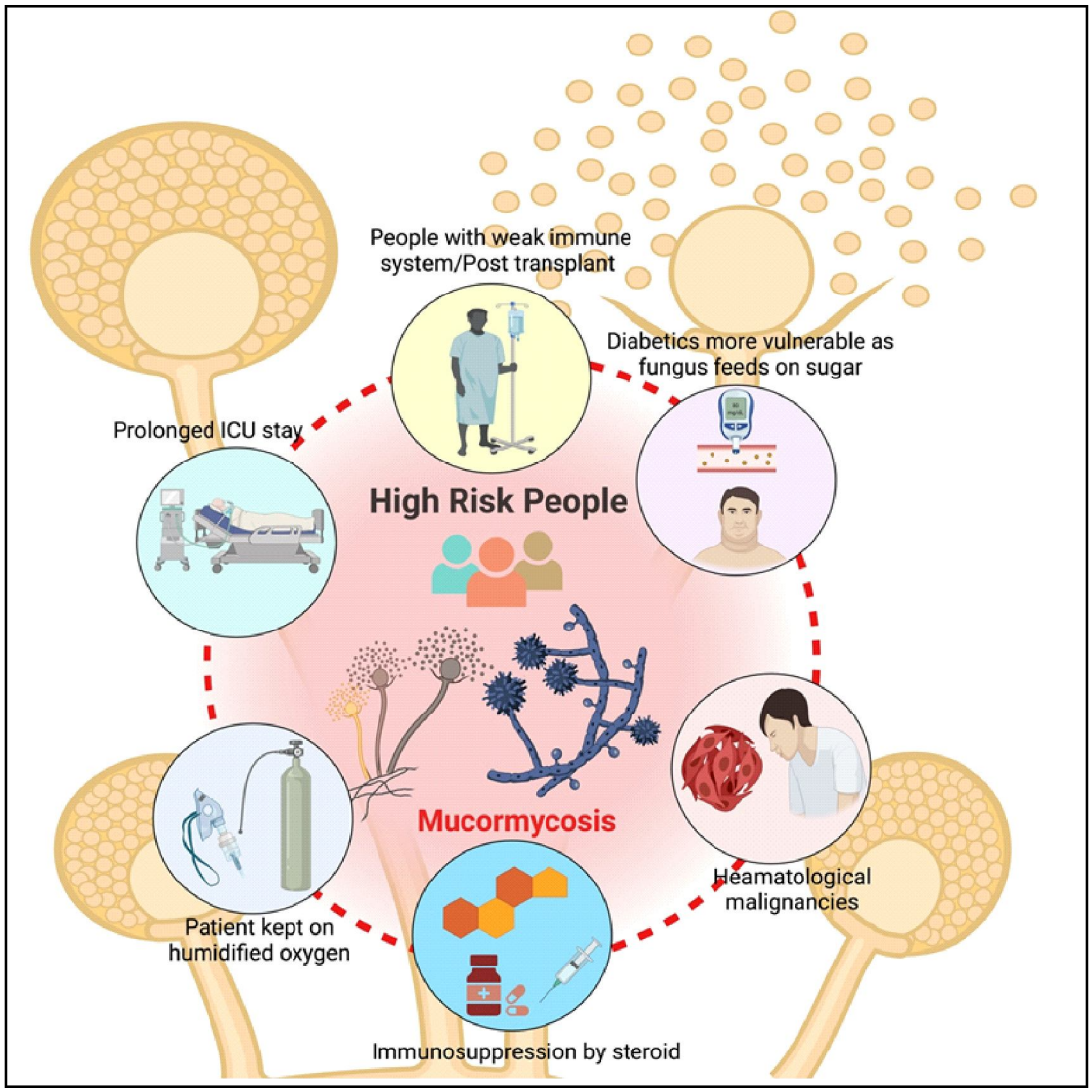


**Figure: Graphical abstract.**

## 2. Mucormycosis types and symptoms

Mucormycosis is also known as zygomycosis. It is a serious, yet rare fungus caused by mucormycetes, a faction of molds. This fungus may be found throughout the environment. For example, the disease may appear in the lungs or sinuses after breathing spores. This type of mucormycosis is prevalent in those who take medications that lessen the body’s potential to fight infections and having severe health issues (Ribes *et al.*, 2000; Petrikkos *et al.*, 2012).

Rhino-cerebral mucormycosis is a sinus infection that can spread to the brain. Mucormycosis of this type is frequent in people with uncontrolled diabetes and kidney transplant recipients (Ahmed *et al.*, 2002; Song *et al.*, 2017). The most common mucormycosis among cancer patients and those receiving stem cell or an organ transplant is pulmonary mucormycosis (Anon‘About Mucormycosis Mucormycosis | CDC’, n.d.). Relatively young children are more likely than adults to develop gastrointestinal mucormycosis, low birth weight children, and those treated with antibiotics, surgery, or medications. This is because they have a lower ability to fight sickness and germs (Vallabhaneni and Mody, 2015; Francis *et al.*, 2018). Cutaneous mucormycosis happens when fungus enters the body through a skin breach (for example, after surgery, different types of

skin trauma or a burn). It is the most prevailing kind of mucormycosis in those who are immune compromised (Anon'About Mucormycosis | Mucormycosis | CDC', n.d.). Finally, disseminated mucormycosis develops when an infection spreads throughout the body *via* the bloodstream. In this type of mucormycosis, infection is usually seen in the brain, although it can also damage the spleen, heart, and skin (Anon'About Mucormycosis | Mucormycosis | CDC', n.d.). Mucormycosis types and risk factors have been shown in Figure 1.

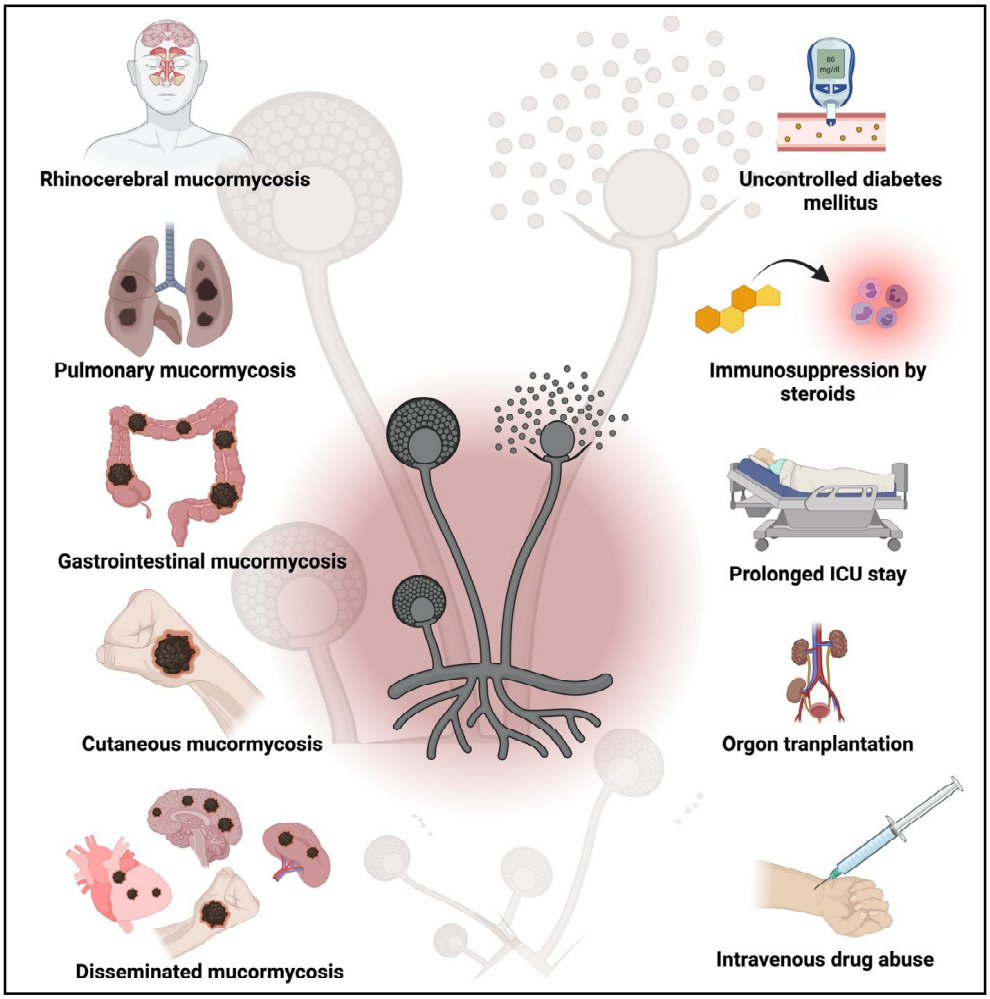


**Figure 1: Mucormycosis type and risk factor.**

Clinicians should be aware that COVID-19 patients may develop invasive fungal illnesses in the future. Warning symptoms cover redness and pain around the nose or eyes, headache, shortness of breath, coughing, fever, altered mental status, and bloody vomits. In addition, as said by the recommendation, mucormycetes infection would be considered, if there is:

- Pleural effusion, chest pain, worsening of respiratory symptoms.
- Necrosis, thrombosis, skin lesion.
- Blurred or double vision with pain.
- Jaw involvement, loosening of teeth.
- Blackish discoloration of the bridge of nose/palate.
- One-sided facial pain, numbness or swelling, local pain on the cheekbone.
- Nasal discharge (blackish/bloody), congestion or sinusitis-nasal blockade (Anon 'mucormycosis COVID symptoms, treatment: 'Black fungus' infection in COVID-19 patients', n.d.; Ribes *et al.*, 2000; Petrikkos *et al.*, 2012).

Experts recommend that all cases of a blocked nose in the case of immunosuppression or COVID-19 patients on immunomodulators should not be acknowledged as bacterial sinusitis.

## 3. Agents of mucormycosis

Mucormycosis is a fungal infection spread by the mucorales group of fungi. The gastrointestinal system, soft tissue, skin, bloodstream, rhinocerebral spaces, sinuses, and lungs are potential infection sites (Reiss, 2006; Anaissie *et al.*, 2009). While for a long time, mucormycosis was thought to be an unusual fungal infection that necessitated extensive medical treatment for the elderly (Roden *et al.*, 2005; Petrikkos *et al.*, 2012; Kontoyiennis *et al.*, 2010; Roilides

*et al*., 2009; Lanternier and Lortholary, 2009; Chayakulkeeree *et al*., 2006). In the current pandemic, the cases of mucormycosis have been rising due to various factors. It demands better management for susceptible people having predisposing conditions such as iron overload, cancer, trauma injury, diabetes and COVID-19 (Garg *et al*., 2021; Chayakulkeeree *et al*., 2006). In individuals with hematological malignancies and transplant recipients, mucormycosis is the second most prevalent fungus. Disseminated infection death rates are unacceptably high, with mortality rates exceeding 90% (Ribes *et al*., 2000).

### 3.1 Uncontrolled diabetes

Mucormycosis is an invasive fungus that typically impacts uncontrolled diabetics patients (Vijayabala *et al*., 2013). Diabetes mellitus alters the body's natural immune response to infection in a variety of ways. Hyperglycemia promotes fungal growth while lowering phagocytic and chemotaxis effectiveness, allowing ordinarily harmless species to flourish in acidic conditions. Mucormycosis caused by *Rhizopus oryzae* is more common in diabetic ketoacidosis patients because these organisms generate the enzyme ketoreductase, which allows them to utilise the patient's ketone bodies (Marx and Stern, 2003). In addition, the capacity of transferrin to bind iron is temporarily disrupted in diabetic ketoacidosis. This mutation disables a critical host defensive mechanism, allowing *Rhizopus oryzae* to thrive (Artis *et al*., 1982). The increased vulnerability to *Rhizopus oryzae* in diabetic mice was studied using diabetic ketoacidosis-induced mice. After being inoculated with *R. oryzae*, all diabetic mice who developed ketoacidosis died within four days.

Furthermore, their blood UIBCs (unbound iron-binding capacity) were considerably lower than normal control mice. This study found that diabetic ketoacidosis causes a reduction in serum UIBC, which promotes *R. oryzae* proliferation *in vivo* (Abe *et al*., 1986). Liu and his team wanted to know how iron and glucose affected the expression of such a receptor. They discovered glucose-regulated protein 78 (GRP78), which they think is a new host receptor that allows *R. oryzae*. It is the most common etiologic mucorales species to invade and harm human endothelium cells, but not *Aspergillus fumigatus or Candida albicans*. Mice with diabetic ketoacidosis (DKA), which are more susceptible to mucormycosis, had shown higher GRP78 expression in their sinuses, lungs, and brains than normal mice. Ultimately, mice with DKA were protected from mucormycosis by GRP78-specific immune serum (Liu *et al*., 2010). These findings point to a distinct vulnerability to mucormycosis in individuals with DKA, laying the groundwork for developing novel treatment approaches for these fatal diseases. A study comprised 28 patients, 3 hematological malignancy patients, 18 diabetes mellitus patients, and 7 solid organ transplant patients. In 7 solid organ transplant patients, 3 had a rejection episode: three more had cytomegalovirus infection before developing mucormycosis.

It was concluded that mucormycosis treatment requires a multispecialty approach. While the underlying risk factors for the solid organ transplant and diabetes mellitus groups differed, the results were comparable (Al-Obaidi *et al*., 2021). Martínez-Herrera and his team reviewed seven cases of ROCM associated to diabetes mellitus. Fungal invasion of the vessels progresses speedily because mucormycosis diagnosis necessitates clinical suspicion and prompt intervention. Its diagnosis is a medical emergency. It should preferably include a direct examination for mycological diagnosis and a culture that grows in 24 h. Imaging studies, such as tomography, are also valuable for determining the degree of damage. Surgical debridement allows for the possibility of cure as well as the collection of material for histological confirmation. The most prevalent differential diagnosis is invasive aspergillosis (Martínez-Herrera *et al*., 2021).

A case of a 44-year-old person was published in Lancet. He reported the reduction in vision of his left eye. Ten days before, he was the recipient of intravenous antibiotics, supplemental oxygen, and corticosteroids due to moderate-severe pneumonia due to COVID-19. The patient said to the doctors that two days before a blackish patch has developed just below the left eye to the level of his mouth. He had a positive history of diabetes without malignancy. Reports of examinations have shown in the Table1 and Laboratory investigations described in Table 2.

**Table 1: Reports of examinations**

| Examinations | Result |
|---|---|
| Temperature | 37°C |
| Pulse | 84 beats per min |
| Blood pressure | 118/82 mm Hg |
| Respiratory rate | 16 breaths per min |
| Pulse oximetry | Oxygen saturation of 96% on room air |
| Visual acuity | 20/20 in his right eye but no perception of light in his left eye. |
| The patient had in his left eye | Exophthalmos, ophthalmoplegia, and chemosis. |

**Table 2: Laboratory investigations**

| Investigations | Result |
|---|---|
| Random blood sugar concentration | 298 mg/dl (normal 140 or below) |
| Glycated haemoglobin A1c | 9·8% (normal 4-5·6) |
| Arterial blood | pH 7·4 (normal 7·35-7·45) |
| Serum bicarbonate concentration | 24 mEq/l (normal 23-30) |
| Mild neutropenia | 1510 neutrophils per µl (normal 1800-6300) |

The patient received intravenous liposomal amphotericin B at a dose of 5 mg/kg per day and continued on insulin infusion due to persistent high blood glucose level. Thorough debridement, a left total maxillectomy, and orbital exenteration were done under a general anaesthesia; however, the patient died 6 days later (Chauhan *et al.*, 2021). Diabetes is a global problem that has grown in prevalence rate over the previous decade. It is linked to significant morbidity and impairment, and mortality. Mucormycosis is a fungal infection that affects severely ill patients of any age and any immunosuppression, particularly diabetics.

### 3.2 Steroids and their administration to COVID-positive patients

The rapidly expanding public understanding of SARS-CoV-2 virology opens a plethora of potential therapeutic targets. WHO is continually revising the COVID-19 therapy regimen (Wahab *et al.*, 2020a). Scientists around the globe are looking for therapeutic or defense trials against the virus due to the lack of medicine. It is a concern for clinicians due to the lack of therapeutic alternatives for its treatment of COVID-19. Clinical practice has resorted to last-resort measures based on shaky facts or assumptions to face the COVID-19. In earlier studies, several anti-inflammatory and antiviral therapies, antimalarial medication, and immune-modulating drugs that affect different elements of inflammation were used and addressed (Vellingiri *et al.*, 2020). Doctors say, 'steroids may help patients with severe COVID-19 infection. Steroids are medicines that save the lives of severe COVID-19 infection patients. Steroids are sometimes administered for individuals who have tested positive for COVID infection. However, there is some ambiguity and commotion around their use. Usage of corticosteroids in COVID-19 patients is debatable. There is a lack of evidence to prove the connection between corticosteroids and increased survival in MERS-CoV-1 and SARS-CoV-1 patients (Russell *et al.*, 2020; Shang *et al.*, 2020).

Corticosteroids are a group of steroid hormones generated by vertebrates'in adrenal cortex with synthetic analogues. Corticosteroids are divided into two main classes: glucocorticoids and mineralocorticoids. They play a role in stress management, immunological responses, inflammatory control, glucose metabolism, protein catabolism, blood electrolyte levels, and other physiological processes. They also decrease the activity of the immunological system (Auld, 1929). Cortisol, corticosterone, cortisone, dexamethasone, betamethasone, and aldosterone are the most prevalent natural and synthetic corticosteroids. Corticosteroid treatment has a long-term effect, which is especially significant in COVID-19 patients with persistent ground-glass opacities. Therefore, recommended regimen of corticosteroids is more than ten days only for severe cases of COVID-19 (Villar *et al.*, 2020; Wahab *et al.*, 2020b). Another reason to prescribe prolonged therapy in COVID-19 patients with pulmonary fibrosis restrict the post-disease fibrosis. Unfortunately, in COVID-19, long-term corticosteroid therapy might unexpectedly result in poor therapeutic results (Mishra and Mulani, 2021). Prolonged corticosteroid treatment may result in what is known as the prolonged COVID syndrome, including tiredness and psychological problems caused by adverse medication relation steroid responses such as psychiatric symptoms, neuromuscular weakness and myopathy (Warrington and Bostwick, 2006; KP *et al.*, 2006).

Misuse of steroids is a precipitating behind black fungus cases. Indiscriminate use of steroids has led to the surge in black fungus cases in India. Treatment has several noticeable adverse effects. It is an important question to raise, what are the indications to administer steroids in COVID patients? Steroids are, in a nutshell, lifesaving. There is sufficient evidence of their efficacy in critical COVID patients who require oxygen, BiPAP, or ventilation who suffer respiratory distress. The viral replication phase is the first week of COVID. Fever, body pain, headache and cold are initial symptoms when steroids should not be administered. Patients have a high fever and self-medicate with steroids or pressurize their doctors to prescribe them. Steroids will temporarily mask the fever symptoms might sort of settle; it might give a sense of false security that patients are getting better. However, in three-five days, patients have a very high fever, cough, respiratory involvement. Results have shown in various cases that many patients who initially took steroids end up with bad pneumonia. The indication for steroids in COVID-19 is in the second week when patients have respiratory distress. Hence, the need for oxygen is high, and the oxygen saturation level is less than 93. At this stage, inflammatory markers in the blood are high, D-dimer, CRP, procalcitonin; all these parameters need to be checked, the ferritin levels also examine simultaneously, and CT scan shows moderate to severe pneumonia.

A study was conducted in Egypt in which researchers observed the same phenomenon of COVID-19 associated mucormycosis (CAM). From March 15$^{th}$ to May 15$^{th}$, 2021, all patients with imaging signs of bone damage and suspected fungal sinusitis after verified COVID-19 evaluation by researchers were included. Regardless of the clinical stage of COVID-19, all patients got corticosteroid treatment due to social media promotion of high-dose steroids (Alfishawy *et al.*, 2021). Experts agree that steroids are a powerful weapon. Still, they must be used cautiously at the right time, dose, and duration in moderate to severe cases, to prevent secondary infections such as the 'black fungus' caused by prolong use of steroids in COVID-19.

### 3.3 Prolonged ICU stays

Intensive care unit (ICU) treatment is required for about 5% of patients with COVID-19 (Wu and McGoogan, 2020). Secondary infections, such as invasive pulmonary aspergillosis (IPA), are a significant concern for these individuals (Lescure *et al.*, 2020). COVID-19 patients who were mechanically ventilated found suspected IPA in almost one-third of cases, a frequency equivalent to that seen in influenza patients (Schauwvlieghe *et al.*, 2018; J *et al.*, 2012; Alanio *et al.*, 2020). Complex surgical and medical issues, numerous invasive operations, extended antibiotic therapy are the leading factors to the rise in fungal infections in ICU (Darouiche, 2009; Blot *et al.*, 2008). Hospitalization and ambulatory care are established risk factors for bacteria, yeasts, and *Aspergillus* species infection. Patients with mucormycosis spend a substantial period in intensive care units, and mortality remains high despite advancements in diagnosis and therapy (Bassetti and Bouza, 2017). Candidaemia is the most common fungal infection. According to the EPIC II research, fungi accounted for 19% of infections identified in ICU patients, including 1,265 ICUs from 75 countries (Vincent *et al.*, 2009). The increasing incidence of mucormycosis with hematological malignancies are due to susceptibility to antifungal agents and high invasive power. A study was conducted to evaluate the epidemiology of mucormycosis in ICU. In between 2008 and 2017, a retrospective multi-centre study was conducted in 16 French ICUs. It was a comparative study in ICU patient's survival. This study was not able to know the factors

associated with ICU survival. This research lacked the overall prognosis of mucormycosis in ICU in hematological malignancies patients (Claustre *et al.*, 2020).

*Zygomycetes*, *Aspergillus* species, *Scedosporium* and *Fusarium* species are rare harmful fungi developed in recent decades. For a positive outcome, timely diagnosis and appropriate treatment are critical. Several laboratory procedures have been developed with blood cultures in the expectation of identifying the disease earlier. The antifungal arsenal has also been increased, providing treatment options suited to the needs of individual patients (Paramythiotou *et al.*, 2014). Therefore, there is a need to identify successive serum samples in galactomannan and *Aspergillus* in lower respiratory secretions in COVID-19 ICU patients. Consultants can choose from the newer azoles, old polyene class, echinocandins and newer azoles. For the proper antifungal drug choice, consider factors such as the patient's clinical state and current co-morbidities, local epidemiology data, and the treatment goal. To identify the best antifungal treatment and drug, there is a need to examine the factors such as local epidemiology data, the patient's clinical state, the treatment goal, and current co-morbidities.

### 3.4 Co-morbidities-post transplant/malignancy

Mucormycosis is a fatal fungal infection that has become increasingly prevalent in recent years. Mucormycosis is now a potential problem for transplant patients, representing 2% and 8% of invasive fungal infections, respectively, in recent cohorts of allogeneic stem-cell and solid-organ transplant recipients. Mucormycosis is most common after transplantation, occurring >3 months afterwards. However, cases have been recorded previously, notably among graft-transmitted infection and liver transplant patients (Fanny Lanternier *et al.*, 2012). Hematopoietic stem-cell transplant and solid-organ transplant recipients may find substantial death rates (Petrikkos *et al.*, n.d.; Skiada *et al.*, 2011; Lanternier *et al.*, 2012). The increased risk of invasive fungal infection in transplant recipients is due to the antibodies used for immunosuppression and powerful T cell-depleting medications (Chamilos *et al.*, 2008). Lungs are the most common infection site in solid organ transplant patients. Prompt diagnosis is complex and has an impact on the result. Surgical and medicinal treatments are used to treat the condition. However, various medicines have been employed in the treatment of mucormycosis. Newer agents have a lot of potentials. Amphotericin B remains the gold standard for mucormycosis treatment (Fanny Lanternier *et al.*, 2012). Most research on mucormycosis in transplant recipients has been retrospective and descriptive, and many have been conducted at a single hospital. Furthermore, the scarcity of current autopsy statistics from transplant patients makes it difficult to accurately assess mucormycosis epidemiological patterns in this population (Hamdi *et al.*, 2014). A probable environment of fungal infection in high-risk peoples have been represented in Figure 2.

One of the most prevalent reason of death after transplantation is post-transplant malignancy, which has controllable and non-modifiable risk factors. However, the current pharmacological arsenal and future immunologic monitoring capabilities hold the promise of customizing post-transplant treatment to lessen the uncertainty of post-transplant malignancy without sacrificing graft survival to maximize transplant results. An interim guideline was released by the World Health Organization (WHO) in September 2020 to use steroids such as dexamethasone and corticosteroids to treat the patients of COVID-19.

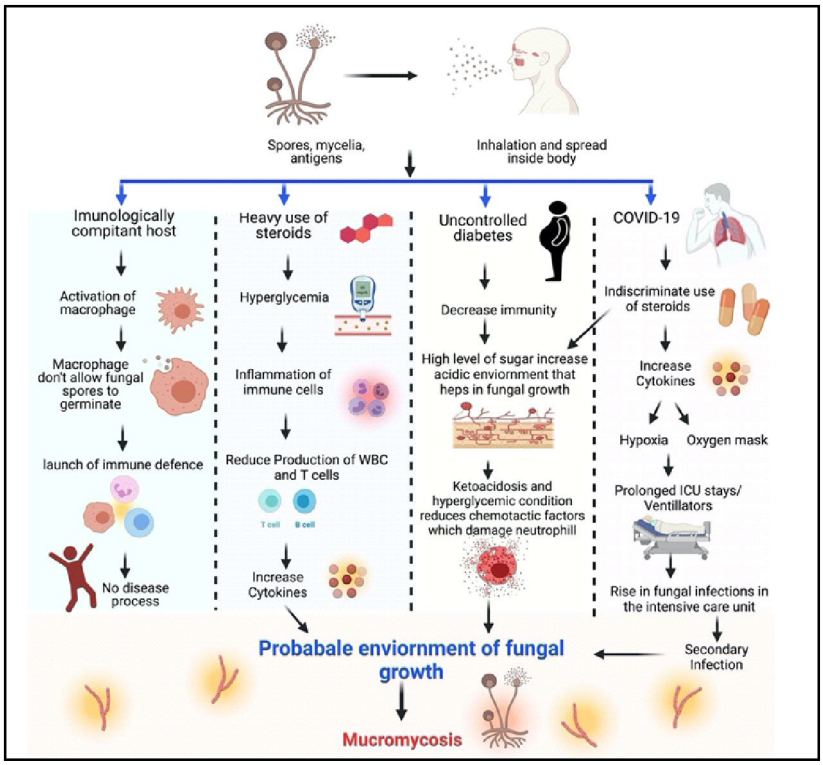


**Figure 2: Probable environment of fungal infection in high-risk peoples.**

It made two recommendations. According to the WHO, the first recommendation is corticosteroids should be administered intravenously or orally to patients with severe COVID-19. The second recommendation of WHO suggested that corticosteroids should not be used in non-severe cases of COVID-19 unless the patient is previously taking for another disease.

- The medicine can be administered once a day for 7-10 days.
- 6 mg dexamethasone, equal to 160 mg hydrocortisone (50 mg every 8 hours or 100 mg every 12 hours), 40 mg prednisone, and 32 mg methylprednisolone should be taken every day (8 mg every 6 hours) (Annane, 2021; Anon‘• According to the WHO, corticosteroids should be administered intravenously or orally to patients with severe COVID-19. - Google Search’, n.d.).

According to the research, although steroids are beneficial in reducing infection linked with inflammation, they “should be administered responsibly and promptly to avoid aggressive viral replication”. For more than 5-7 days, use of steroids should be restricted for those who have breathing trouble, persistent fever and increasing cough related inflammation in the airway. If, the patient’s condition does not improve, the dosage should be reduced over time, and a new treatment approach should be established. While prescribing “higher doses of steroids to diabetic patients,” physicians “should be careful about secondary infections”. India is the world’s diabetes capital. Random use of steroids for diabetes, both known and suspected, may result in superadded infections or breakthrough bacterial and fungal infections. Dexamethasone and methyl/prednisolone are the steroids utilized in COVID-19. A systemic inflammatory response in individuals with severe COVID-19 can lead to lung injury and multisystem organ failure. On the other hand, steroids’ powerful anti-inflammatory properties may help to reduce negative side effects.

### 3.5 Use of industrial oxygen

There are several uses of oxygen, but industrial use of oxygen is far different from medical use. There was a massive demand for oxygen in the second wave of COVID-19; therefore, industrial oxygen was redirected to medical use. The same cylinder used in industry is diverted to health facilities and hospitals. According to WHO’s guidelines, the purity and quality of industrial oxygen are far different from medical use oxygen. Industrial oxygen could be contaminated in production, storage, and distribution because there is no need for extra care for it (Anon ‘Health product policy and standards’, n.d.). Industrial oxygen cylinders are unsuitable for medical purposes because these cylinders are contaminated due to storage in a dusty environment, unclean cylinders and prone to micro leaks. On account of these causes, industrial cylinders may not be used for medical purposes. Industrial cylinders undergo various processes such as sealing micro leaks, deep cleaning, disinfection, and testing before medical use. Consequently, there was an acute shortage of oxygen supply in the second wave of COVID-19. Time and cost were involved in following the strict protocol to convert industrial cylinders to medical use. These strict guidelines and protocols were not followed at various levels, increasing the risk of opportunistic fungal infection (Bhatia, 2021). It happened in India because there is no law to make accountable to anyone. It is the need of time to take precautionary measures at various stages of production and distribution. Regulatory bodies of medical devices and medicines must be responsible for assuring protocols of converting the industrial cylinders to medical use for well-being. The government must give authority. Health facilities need consent from the regulatory bodies before using the industrial cylinders in medical use and must follow strict protocols. Medical staff dealing with the different instruments of oxygen supply should be trained to use instruments such as catheters, ventilators, tubings, fittings and humidifiers. They should know the process of sterilization and fumigation and assure the use of sterile water for humidification. All the mucormycosis cases should review and find out the connection between industrial oxygen and mucormycosis.

## 4. Cases of mucormycosis

Mucormycosis is caused by underlying immune system disorders such as prolonged use of steroids, diabetes, solid organ transplantation and chemotherapy (Park *et al.*, 2011; Song *et al.*, 2017; Lanternier *et al.*, n.d.). Mucormycosis can also occur due to severe burns, recurrent traumas, or specific medical treatments (Blandine Rammaert *et al.*, 2012; Bitar and Che, 2013). Mucormycosis is a fatal invasive fungal disease that occurs primarily in diabetic patients without or with other underlying disorders such as solid-organ transplantation or haematological malignancies. Rhino-orbital cerebral mucormycosis (ROCM) in immunocompromised and diabetic individuals is an uncommon but lethal fungal infection. Only a few examples of bilateral participation in ROCM have been recorded (Jiang *et al.*, 2016; Denning and Stevens, 1990; De la Paz *et al.*, 1992). The infection spreads from the nasal mucosa to the sinuses, orbit, and brain in ROCM, which is generally one-sided (Lam and Yuen, 2019). The primary location of mucormycosis is the ROC region, although the lack of symptoms may contribute to a postponed diagnosis. Any instance in diabetic individuals confirmed non-bacteriological sinusitis, even if there is no ketoacidosis, should raise the possibility of mucormycosis (Rammaert *et al.*, 2012).

Five patients’ medical records were analysed with ROCM between January 1995 and December 2007. Tissue biopsies were performed on all patients. It was found in histologic sections presence of non-septate hyphae of the order mucorales. There were five patients, two women and three men ranging in age from 27 to 61, who had diabetes. Five patients of exophthalmia, four patients with face edema, four patients with periorbital cellulitis, and cranial nerve palsy were the most common symptoms in four patients. All the patients had diabetic ketoacidosis, and a CT scan indicated that they all had rhino-orbital-cerebral involvement. Amphotericin B was administered intravenously to all the patients. Surgical debridement of necrotic tissue was performed on four individuals. Two of the patients made it out alive. The outcome of the study has shown that in diabetic individuals, mucormycosis is almost always deadly. Therefore, imaging, and histological data should be used to make an early diagnosis. This study also advised that Amphotericin B must be administered early with aggressive surgical debridement to reduce mortality (Toumi *et al.*, 2012).

In another case report, eleven cases were analysed of ROCM with OAS (orbital apex syndrome). Mucormycosis was shown to be associated with type 2 diabetes in nine instances, a kidney transplant in one case of a traffic accident injury. Anterior rhinoscopy in all patients indicated nasal necrotic lesions or palatine; at the same time, three of them had transethmoidal optic nerve decompression. CT scan of every patient has shown rhino-orbital-cerebral involvement. Amphotericin B was administered intravenously to all the patients. Necrotic tissue was surgically debrided in nine cases.

Three patients had been survived after the clinical management. These cases concluded that ROCM is a life-threatening illness requiring comprehensive treatment (Jiang *et al.*, 2016).

A retrospective study evaluated the different stages of ROC mucormycosis of treatment outcomes and clinical features. This retrospective case series examined the case histories of 34 patients with a histological diagnosis of ROC mucormycosis treated between 1992 and 2000. There were three clinical phases identified, as well as three therapy groups. In the first clinical stage, patients with limited sino-nasal disease underwent sino-nasal debridement (Treatment group A). In the second clinical stage, patients with minor rhino-orbital disease underwent either sino-nasal debridement alone (Treatment group A) or orbital exenteration in addition to sino-nasal debridement (Treatment group B). Clinical stage second, patients with rhino-orbito-cerebral disease did not undergo any surgical procedure (Treatment group C). Thirty-three patients were administered amphotericin B intravenously. "Treatment success" (disease-free, stable patient with metabolic abnormality under control) and "Treatment failure" (disease-free, unstable patient with metabolic abnormality under control) were the outcomes for each group. At last, it was concluded that sinus debridement is required for rhino-orbito-cerebral mucormycosis. Early diagnosis necessitates a high level of suspicion. In individuals whose metabolic derangement is promptly controlled and orbital engagement is non-progressive, there is a clear role in retaining orbits (Nithyanandam *et al.*, 2003).

Shatriah and his team reviewed eleven cases of ROCM in immunocompetent hosts in PubMed from 2000 to 2011. All these reviews have shown that both the genders between 16 and 59 years were equally affected. The emerging pathogen cause of ROCM is *Apophysomyces elegans*. In conclusion of this study, researchers said that ROCM in immunocompetent patients is forever confusing and possibly the reason for the delay at the beginning of treatment. It is necessary to warn the ophthalmologist of the evolution of this rare disease in healthy individuals (Shatriah *et al.*, 2012). A 59-year-old immunocompetent white man was injured while cleaning an air conditioner. This injury did not respond to antibiotics and cause orbital cellulitis. Biopsy and imaging studies had shown mucormycosis. This agent was causing this case of ROCM. It is concluded that ROCM has shown orbital inflammation associated with retinal or orbital infarction and multiple cranial nerve palsies despite their immunologic status. It is suggested that early management could be done with appropriate systemic antifungal agents and appropriate surgery (Fairley *et al.*, 2000). Effective treatment of ROCM may include; (i) prompt antifungal therapy, (ii) early diagnosis, (iii) reversal of underlying risk factors, (iv) surgical debridement where applicable (Spellberg *et al.*, 2005). Fortis Hospital Mulund, a tertiary care center in Mumbai that was admitting COVID-19 patients since the pandemic. An ICU consultant stored data electronically and looking specifically at the incidence of mucormycosis and strictly followed the protocol of steroid use, monoclonal antibodies, glycemic control and diabetes mellitus. COVID-19 patients were retrospectively assessed in this study. ICU and hospital admitted patients were analyzed in the context of mucormycosis. Maharashtra state task force and local guidelines were followed for treatment protocol. During the hospital stay and immediate outpatient department follow-up, no cases of mucormycosis were reported. Following the guidelines of the state government, low dose steroids were given to patients, which included a nurse-led strict glycemic control regime (blood glucose levels were maintained between 140 and 180 mg/dl throughout the ICU stay and were consistently achieved in 842 (82%) patients), immunomodulatory drugs were used minimal, like monoclonal antibodies. In a tertiary care specialized COVID-19 facility, rigorous adherence to a low-dose steroid program combined with stringent glucose management managed to eliminate the danger and occurrence of mucormycosis (Mulakavalupil *et al.*, 2021).

A lady of 62 years was admitted to ICU with a combination of emphysema, bilateral ground-glass opacities with crazy paving, and peripheral nodular consolidations on the contrast-enhanced CT. Despite being prone, the patient required veno-venous extracorporeal membrane oxygenation for rescue (ECMO). In BALF, PCR for SARS-CoV-2 and human metapneumovirus (hMPV) were also positive. Despite being prone, the patient required veno-venous extracorporeal membrane oxygenation for rescue (ECMO). In BALF, PCR for SARS-CoV-2 and human metapneumovirus (hMPV) were also positive. The patient experienced significant intrapulmonary bleeding from the right main bronchus, which was stopped with cold lavages and tranexamic acid instillation. The BALF culture developed *Aspergillus fumigatus* and tested positive for galactomannan; therefore, therapy with intravenous voriconazole was started (Koehler *et al.*, 2020). According to research, severely sick COVID-19 patients are more prone to have *Aspergillus* co-infection, which will undoubtedly raise death rates even further. A summary of mucormycosis cases and management has been shown in Table 3.

## 5. Management of mucormycosis

Although, guidance on complicated interdisciplinary management has the potential to enhance prognosis, approaches vary by healthcare environment. In view of the European Confederation of Medical Mycology's "One World One Guideline" effort, authors from 33 countries across all United Nations regions analyzed published data on mucormycosis treatment and offered consensus guidelines that addressed regional variances. High-dose liposomal amphotericin B is suggested first-line therapy, while intravenous or delayed-release tablet posaconazole are moderately indicated and intravenous isavuconazole. The use of both triazoles as salvage therapy is strongly advised. Because of its high toxicity, amphotericin B deoxycholate is not recommended, although it may be the only alternative in resource-constrained situations (Cornely *et al.*, 2019). Present recommendations in haematology are confined to specific patient categories or a geographic location, or they need to be updated (Skiada *et al.*, n.d.; Blyth *et al.*, 2014; Cornely *et al.*, 2014; Kung *et al.*, n.d.; Tissot *et al.*, n.d.). It is uncertain how long treatment for mucormycosis will take. However, if the immune defect and neutropenia are a resolved: for example, and diabetes is under control, then immunosuppression can be stopped or tapered. Therapy can be continued until signs and symptoms of infection have resolved significant radiographic improvement has occurred. Isavuconazole was given intravenously or orally for 84 days as a first-line or salvage therapy (Cornely *et al.*, 2019; Marty *et al.*, n.d.). Treatment duration for posaconazole oral suspension trials ranged from one week to over three years, with an average of about six months (Kim *et al.*, 2016; Ma *et al.*, 2015; Burik *et al.*, n.d.; Greenberg *et al.*, 2006; Larkin and Montero, 2003; Cornely *et al.*, 2019). Therapeutic action and rapid diagnostic such as radiological, surgical, laboratory-based team and multidisciplinary medical consultants are required to enhance the survival rates (Vaughan *et al.*, 2018).

**Table 3: Summary of mucormycosis cases and management**

| No. of cases | Gender history | Clinical | Site of infection/ susceptibility testing | Fungus species | Management drug | References |
|---|---|---|---|---|---|---|
| 174 | 76% male | Major | Rhinocerebral underlying diseases were diabetes (43.1%) | Rhizopus | Posaconazole and lipid amphoterincin B | (Song *et al.*, 2017) |
| 74 | Sex ratio M/F 1.96 | 60 cases (81%) were immuno compromised | lungs (39.2%), and the skin (20.3%) | Rhizopus genus in 22 cases (29.7%), Lichtheimia genus in 19 cases (25.7%), Rhizomucor genus in 14 cases (18.9%), Mucor genus in 9 cases (12.2%), Cunninghamella genus in one case (1.4%) | L-AmB, L-AmB with caspofungin, L-AmB with posaconazole | (Claustre *et al.*, 2020) |
| 230 cases | 60% men | Haematological malignancies (44%), trauma (15%), haematopoietic stem cell transplantation (9%) and diabetes (9%) | Pulmonary (30%), rhinocerebral (27%), soft tissue (26%) and disseminated disease (15%) | Rhizopus spp. (34%), Mucor spp. (19%) and Lichtheimia (formerly Absidia) spp. (19%) were most identified. | Amphotericin B 39% formulations, 7% posaconazole and 21%, received both agents; 15% of patients received no antifungal therapy | (Skiada *et al.*, 2011) |
| 5589 | | Multiple transplants, neutropenia | Lungs in 191 patients, sinuses in 22, and other sites (liver, gut, or skin without further organ involvement) in 5. Probable IA involved the lungs in 106 patients, sinuses in 16, and other sites in 2. Possible IA involved the lungs in 27 patients, sinuses in 5, and liver in 1 | Aspergillus species (69%) | Amphotericin-B deoxycholate or lipid formulations of amphotericin-B | (Marr *et al.*, 2002) |
| 1 | 79-year-old Latino male | Diabetes mellitus and hypertension | lung tissues | *Rhizopus arrhizus* and *Aspergillus fumigatus* | L-AmB 400 mg | (Johnson *et al.*, 2021) |
| 1 | 74-year-old patient | Reflux, polyarthrosis, stopped smoking 20 years ago | Chest, pulmonary | *Aspergillus fumigatus* | amphotericin B 0.5 mg/l, anidulafungin and micafungin <0.016 mg/l, itraconazole 16 mg/l, voriconazole 2 mg/l and posaconazole 0.5 mg/l. | (Meijer *et al.*, 2020) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 31 | | Three patients had pre-existing lung diseases | Chest, pulmonary | *Aspergillus fumigatus* in five patients | Voriconazole and anidulafungin combination therapy was initiated in five patients, and one patient received liposomal amphotericin B | (van Arkel *et al.*, 2020) |
| 1 | 64-year Female | Lap. cholecystectomy for cholecystitis, Arterial hyper-tension, Obesity with sleep apnea (BMI 31.5), Hyper cholester-olemia, Ex-smoker (30 PY; 5 y previously) Moderate COPD (GOLD 2), Inhalation of steroids | Azole susceptible | *Aspergillus fumigatus* | Voriconazole iv (6/4mg/kg BW twice daily) | (Koehler *et al.*, 2020) |
| 5248 | - | 915 received steroids, and 417 had diabetes as existing co-morbidity | No susceptible | No sign of any mucormycosis | No need for any antifungal drug | (Mulakavalupil *et al.*, 2021) |
| 1 | 44-year-old man | A moderately severe pneumonia caused by SARS-CoV-2.; diabetic | Case complained of a blackish discolouration extending just below his left eye upto the left side of his face to the level of his mouth | *Rhizopus arrhizus* | I/V liposomal amphotericin-B at a dose of 5 mg/kg/ day; an insulin infusion was also continued because of persistent hyperglycaemia | (Chauhan *et al.*, 2021) |

## 6. Plants having antifungal activity

In the last several decades, there has been a worldwide increase in the prevalence of fungal infections, as well as a growth in the resistance of specific fungus species to various fungicides used in medicine. The majority of commonly used antifungal medications have various side effects in terms of toxicity, effectiveness, and cost, and their widespread usage has resulted in the development of resistant strains (Kumar Mishra *et al.*, 2020; Ahmad *et al.*, 2020; Hussain *et al.*, 2012). The area of herbal medicine has grown at an exponential rate during the last few decades. Because of its natural origins and fewer adverse effects, it has become popular in both developed and developing countries. In an experimental study, a herbal gel containing *Ipomoea carnea* Jacq. methanolic leaf extract was prepared and evaluated for antifungal activity. The gel might be utilized to treat cutaneous aspergillosis, face skin symptoms caused by Penicillium, cutaneous mucormycosis, and other skin diseases, according to the findings of this study (Kaushik *et al.*, 2020; Alsayari and Wahab, 2021; Wahab *et al.*, 2021). Many plants have been used to cure fungal infections, as described in ancient Chinese medical texts and current literature. A study was conducted to examine the antifungal activities of Traditional Chinese medicine (TCM) using consistent methods and standards. Twenty-two herbal extracts worked against *Candida albicans*, 52 having inhibitory effects against *Cryptococcus neoformans* and six against *Aspergillus fumigatus*. *Phellodendron chinense, Syzygium aromaticum, Neopicror hizascrophulariiflora, Rosa chinensis* and *Curcuma longa* exhibited broad-spectrum antifungal activities. Flavonoids and gallic acid were the primary antifungal components of *Rosa chinensis*. These compounds have shown antifungal effects that were both synergistic and additive (Jiang *et al.*, 2020). Fifteen plants leaves extracts were examined at MIC to find the antifungal activities against the opportunistic pathogen *Candida albicans* isolated from oral cavity infections.The best inhibitory effects were given by the herbal extracts of *Zingiber officinale, Withania somnifer, Lawsonia inermis, Cymbopogon citrates, Curcuma longa and Ganoderma lucidum*, and these herbs have the potential to inhibit the growth of *Candida albicans* (Samadi *et al.*, 2019; Ahmad *et al.*, 2021). Selina-1,3,7 (11)-trien-8-one and selina-1,3,7 (11)-trien-8-one are the two components of *Eugenia uniflora* that exhibited antifungal activity. The performance of *E. uniflora* essential oil was considered as a fungistatic agent (dos Santos *et al.*, 2018; Alsayari *et al.*, 2021; Wahab *et al.*, 2021). Many others plants have exhibited antifungal properties such as *Mimosa tenuiflora, Aquilegia vulgaris, Aniba panurensis, Alibertia macrophylla, Ajania fruticulosa, Parapiptadenia rigida, Persea americana, Schinus terebinthifolius, Piptadenia colubrina, Curcuma longa* and *Psidium guajava*.

## 7. Conclusion

Agents of mucormycosis are different with geographical regions as in North America and Europe hematological malignancy followed by diabetes, trauma and SOT but in Mexico and India uncontrolled diabetes is the most common cause (Serris *et al.*, 2019; Corzo-León *et al.*, 2018). A large number of COVID-19 cases in India perhaps contributing to the present increase in mucormycosis patients. During COVID-19's second wave, the number of mucormycosis cases spiked substantially. Several additional risk aspects for mucormycosis include: neutropenia, HIV, organ transplant and malignancy. The development of mucormycosis is influenced by diabetic ketoacidosis and steroids. A rise in the cases is related to uncontrolled use of steroids and diabetes in the current scenario. Surgical debridement, antifungal drugs and early detection are the therapies to control mucormycosis. There is a need to differentiate other bacterial infections and aspergillosis from mucormycosis. In the current epidemiological conditions, clinicians should be aware of the higher likelihood of contracting this potentially deadly disease and judiciously use steroids in all patients**.** There is a need for data-based clinical practice. Before using the medications, there is a need to collect data on their favorable use. Many platforms designed for practical research, such as recovery and principle, have emerged to inform clinicians. Reports show that strict protocol for following steroids and tight control of glycaemia can help avoid mucormycosis. COVID-19 patients' disease severity and risk of mortality will be significantly reduced, if this fungus is identified early and further investigated. After assessing multiple cases, clinicians should be cautious that in severely COVID-19 cases, combined mucormycosis and pulmonary aspergillosis can result in secondary COVID-19 consequences. More research should be conducted on post-COVID-19 mucormycosis patients in different settings to explore the risk factors further. The findings of studies must be validated in clinical trials to determine the probable role of post-COVID-19 mucormycosis.

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## Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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