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Review

Mucormycosis in COVID-19: modifiable risk factors and its mitigation in India

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Abstract
While combating the second wave of COVID-19, India has now been afflicted by another epidemic caused by mucormycosis, a life-threatening opportunistic infection. Due to their immune-suppressed status, COVID-19 patients in India are now more likely to develop mucormycosis during or after treatment. Uncontrolled diabetes, irrational use of steroids, as well as the severity of COVID-19 can all contribute to the growth of mucormycosis. Risk mitigation strategies that could be used to control the rise of mucormycosis-related COVID-19 patients should be evaluated. The purpose of this article is to explore the modifiable risk variables that are involved in the medical management of COVID-19 patients, as well as the mechanisms through which they raise the risk. This overview also includes a brief discussion of mycology and how the disease pattern varies depending on the regions of the body affected. In this article, we detailed about the early detection and treatment of mucormycosis in COVID-19 patients.

Keywords
Mucormycosis, COVID-19, Risk factors, Mycology

1. Introduction

COVID-19 is a rapidly developing healthcare hazard that began as a cluster pneumonia outbreak in Wuhan, China. India has been among the countries severely hit by the pandemic (Hiscott et al., 2020). During the second wave of COVID-19, the country was hit by another epidemic, mucormycosis, widely known as “Black Fungus” which has wreaked havoc on the healthcare system, and because of their immunosuppressed status, COVID-19 patients are more susceptible to bacterial and fungal infections. The rise in prevalence of diabetes Mellitus (DM) in the Indian population makes these COVID-19 patients more prone to develop mucormycosis. A meta-analysis of 600 publications from 2000 to 2017 comprising 851 cases of mucormycosis worldwide cited the following risk factors for mucormycosis: DM (40%), trauma (33%), hematological malignancies (HemeM) (32%), diabetic ketoacidosis (20%), neutropenia (20%), no underlying disease (18%), solid organ transplant (14%), burns (11%), natural disasters (5%) (Jeong et al., 2019). In Asia, DM is the most common risk factors of mucormycosis (Prakash and Chakrabarti, 2019). Surveillance of 15 tertiary hospitals in Australia identified 74 cases of mucormycosis from 2004 to 2012; only 8 patients (10.8%) were previously healthy (Kennedy et al., 2016).

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Globally, India was reported with maximum number of mucormycosis cases (71%) with an estimated prevalence of 140 cases per million population (Prakash et al., 2019). Moreover, India has the second-large of the population aged 20–79 years with DM (John et al., 2021). In reality, DM is the single most common risk factor for mucormycosis in India, with a report of over 50% of cases of mucormycosis. A multicenter study on mucormycosis in India reported 57% of patients with uncontrolled DM and 18% by diabetic ketoacidosis (Prakash et al., 2019).

The spike in mucormycosis could be linked to poor care of pre-existing diabetes, overuse of steroids, and prolonged Intensive Care Unit stays. Post-tuberculosis, chronic renal failure, and stay in intensive care units are new risk factors for the disease especially in developing countries (Prakash and Chakrabarti, 2019). This review will be helpful in giving comprehensive coverage of the risks involved with medical treatment, as well as how to avoid them. This article focuses on the risk factors for Mucormycosis in COVID-19 patients, particularly in India, where the frequency is relatively high when compared to other countries. This study used published case reports and case series from India to show risk factors for Mucormycosis in COVID-19 patients, and it also raised a question for future research on mechanical ventilation-associated Mucormycosis in COVID-19 patients.

2. Mycology

Mucormycosis is one of the most lethal fungal diseases caused by Mucorales. The most commonly isolated Mucorales from humans are from the genera *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Absidia* (Hoffmann et al., 2013). *Rhizopus* is the most common causative genus among Mucorales in human infections, with a fatality rate of 46% (Revannavar et al., 2021). Depending on the species, the site of infection would be different. The angioinvasive features of the fungus are assumed to be due to a link between a protein in the fungus and a protein called GRP78 on the endothelium of the host (Ibrahim et al., 2012). The interaction is depicted in full in the Figure 1.

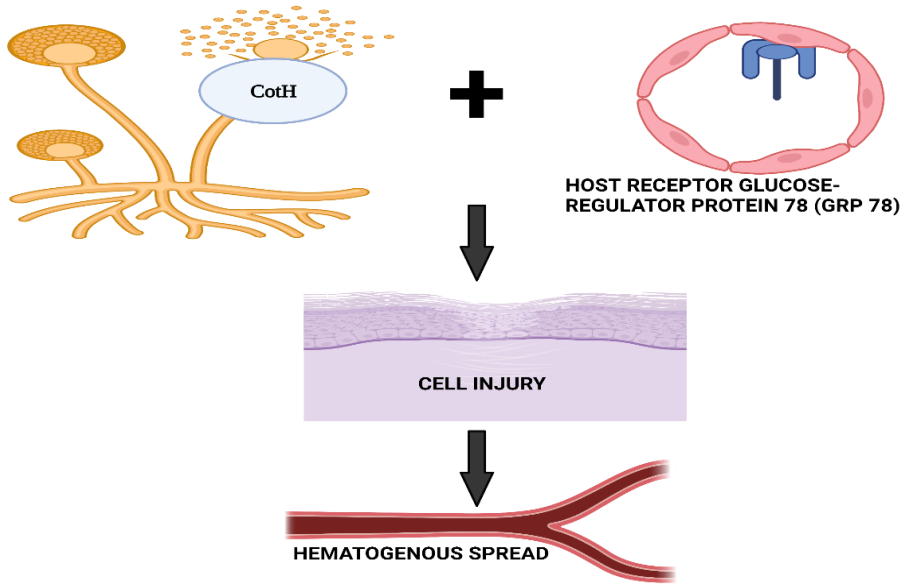

Fig. 1 - Interaction between spore coat protein (COTH) and GRP78 leading to angioinvasion by fungi.

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3. Epidemiology

Looking into the general epidemiological data of mucormycosis, Webb et al. (2018) in a large network of hospitals and clinics in the USA from 2006 to 2015, only 1.1% of 3,375 invasive fungal infections (IFIs) were due to Mucorales and incidence was 0.3 cases/100,000 per year. The underlying cause seems to be DM (36.1%), immunosuppressive therapy (61.1%), hematopoietic stem cell transplant (HSCT) (11.1%), HemeM (19.4%) (Webb et al., 2018). Another study conducted by Kontoyiannis et al. (2016), reported that there were 555 mucormycosis-related hospitalizations among 47 million inpatients admitted (prevalence of 0.12 per 10,000 discharges) from 560 hospitals in the USA from 2005-2014. National Hospital Discharge Data Base survey of France, from 2001 to 2010 found that 1.5% of 35,876 invasive fungal infections were due to mucormycosis (Bitar et al., 2014) and the incidence of mucormycosis in France was 0.7 per million and 1.0 per million in 2006 (Bitar et al., 2009). A study in Spain reported 19 cases of mucormycosis were diagnosed from 2007 to 2015 (incidence 3.2 per 100,000) (Guinea et al., 2017).

During the second wave of COVID-19 in May 2021, India accounted for nearly half of all cases worldwide. Although mucormycosis is rare, the incidence has increased globally over the past two decades, 13 particularly in France, Belgium, Switzerland, and India. However, India has the highest number of mucormycosis occurrences when compared to other countries (Singh et al., 2021). The actual incidence of mucormycosis in India is unknown due to a scarcity of population-based investigations. The second wave of COVID-19 had a significant impact on India, with the peak number of daily recorded cases being slightly more than 0.4 million on May 7, 2021, and has subsequently fallen. Even though the number of newly reported cases has reduced, India still contributed to approximately 45% of the new cases detected globally and nearly 34% of the deaths globally during the third-week of May 2021. The accurate incidence/prevalence could be more in mucormycosis, due to undiagnosed cases, difficulty in collecting the sample from deep tissue and low sensitivity of diagnostic methods.

The Leading International Fungal Education (LIFE) portal has assessed the burden of severe fungal infections globally. Conferring to approximation, the annual prevalence of mucormycosis could be around 10,000 cases globally, barring India. Subsequently, the addition of Indian data, the estimate of mucormycosis rise to 910,000 cases globally. A computational-based approach assessed the prevalence of mucormycosis at 140 cases per million populations in India, with the prevalence ranging between 137,807 cases to 208,177 with the mean of 171,504 (SD: 12,365.6; 95% CI: 195,777–147,688) and a mean attributable mortality at 65,500 (38.2%) per year (Prakash et al., 2019). Because India has the world's second-largest diabetic population, the Indian population is more vulnerable to mucormycosis. The number of cases of mucormycosis increased during the second wave of COVID-19, worsening the situation in hospitals. As of 28th May 2021, the total number of mucormycosis cases reported in India was 14,872. Gujarat leads the way with 3726 cases, followed by Maharashtra. Mucormycosis has also been reported in the states of Rajasthan, Andhra Pradesh, Karnataka, Haryana, Madhya Pradesh, Uttarakhand, and Delhi (Raut et al., 2021.) As announced by Mr. Harsh Vardhan, the former Health Minister of India, there are over 40,000 cases of mucormycosis reported as of 28 June 2021 (Ministry of Health, 2021). Mucormycosis has been declared an epidemic in several Indian states and has been classified as a notifiable disease.

4. Route of exposure

Inhalation, ingestion, and open wounds exposure of spores are the most typical methods of infection. Inhalation spreads spores in pulmonary and rhino-orbital-cerebral mucormycosis, whereas ingestion or wounds spreads spores in gastrointestinal and cutaneous mucormycosis. The cilia will propel the

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spores to the throat, where they will be removed by the gastrointestinal tract. Infected nasal turbinate or alveoli develop in vulnerable patients (Ibrahim et al., 2012). The spores are distributed in the bloodstream due to their angio-invasive properties.

5. Clinical presentation of mucormycosis in COVID-19

In susceptible individuals, the infection is characterized by ischemic necrosis of the tissue caused by angio-invasion by the hyphae following spore inhalation. Mucormycosis is classified into several types relying on the affected area (Table 1), such as rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, renal, and diffuse mucormycosis (Nishanth et al., 2020). Clinical manifestations will also vary depending on location (John et al. 2021).

The most common type of mucormycosis in COVID-19 patients is rhino-orbital cerebral mucormycosis, followed by pulmonary and gastrointestinal mucormycosis. Patients with gastrointestinal mucormycosis have a poor prognosis when compared to the former. Patients with pulmonary mucormycosis were more likely to develop disseminated mucormycosis (Singh et al., 2021).

Table 1 - Classification of mucormycosis based on location and their manifestations (John et al., 2021).

Type of mucormycosis	**Clinical presentation**
Rhino-orbital cerebral mucormycosis	Fever, ulceration or necrosis of the nose, swelling around the eyes or on the face is known as periorbital swelling. Vision impairment, ophthalmoplegia, sinusitis, headache
Pulmonary mucormycosis	Pneumonia, fever with hemoptysis
Gastrointestinal mucormycosis	Abdominal pain, hematemesis, peritonitis
Cutaneous mucormycosis	Localized hardening of the tissue, single, painful, ecthyma like lesion
Renal mucormycosis	Flank pain, fever

6. Predisposing factors of mucormycosis in general and COVID-19

The general predisposing factors for mucormycosis is poorly controlled DM, hematological malignancy, neutropenia, hematopoietic stem cell transplantation (HSCT), solid organ transplant recipients, immunosuppression or chemotherapy, autoimmune or rheumatic disorders, human immunodeficiency virus infection, peritoneal dialysis, iron overload states, malnutrition, trauma, burns, and prior receipt of "voriconazole" (Reid et al., 2020) out of which the most common predisposing factors for the occurrence of mucormycosis is found to be Diabetes mellitus, steroid therapy, and uncontrolled severe COVID-19.

7. The mechanism by which each risk factor can induce mucormycosis (Fig. 2)

7.1. Uncontrollable DM

It is unsurprising that India accounts for around half of all mucormycosis cases worldwide, given that it is the country with the second-highest number of diabetes patients (Prakash et al., 2019). The risk of acquiring hyperglycemia in people with pre-existing DM is extremely significant. This can be explained by a problem with pancreatic islets, which can lead to insulin resistance. In the diabetic population, natural killer cells, such as TNF, are reduced, whereas the number of pro-inflammatory macrophages increases (Prakash et al., 2019). An increase in blood glucose levels can suppress the

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antiviral response and on the other hand increased serum iron levels in diabetic ketoacidosis create a favorable environment for the formation of spores.

7.2. Steroid therapy-induced immunosuppression and hyperglycemia

Steroid therapy, which typically lasts 2-14 days, can cause hyperglycemia. The sequestration of CD4+ T-lymphocytes in the reticuloendothelial system is one process by which corticosteroids cause immunosuppression (Barshes et al., 2004). Steroids can reduce islet cell insulin synthesis while increasing endogenous glucose production, leading to hyperglycemia. It also impairs phagocyte function, making invasive infections more likely (Tamez-Pérez et al., 2015).

7.3. Severe COVID-19

The risk of mucormycosis increases as the severity of the ailment worsens. In this state, the IFN-γ response is delayed, and the inflammatory response is heightened. Because of the cytokine storm, a fertile environment for spores is created. A prolonged hospital stay is another factor that can prolong the severity and risk of infection. In severe COVID-19, the number of lymphocytes decreases, SARS-CoV-2 infection may affect CD4+ and CD8+ T-cells, which are involved in the pathological process of COVID-19 infection. Mucorales-specific T-cells (CD4+ and CD8+) produce cytokines such as interleukin (IL) 4, IL-10, L-17 and interferon-gamma (IFN-γ) that damage the fungal hyphae. As a result, lymphopenia could increase the risk of developing mucormycosis (Revannavar et al. 2021; Singh et al., 2021).

The major reason that Mucorales spores appear to proliferate in people with COVID-19 seems to be high blood sugar (new-onset hyperglycemia, diabetes steroid-induced hyperglycemia), oxygen deprivation (hypoxia), reduced phagocytic activity owing to immunosuppression (steroid mediated, SARS-CoV-2 mediated or background comorbidities) acidic medium (diabetic ketoacidosis [DKA]), metabolic acidosis, increased iron levels (increased ferritins), and in combination with several other factors such as prolonged hospitalization with or without mechanical ventilation. (Singh et al., 2021).

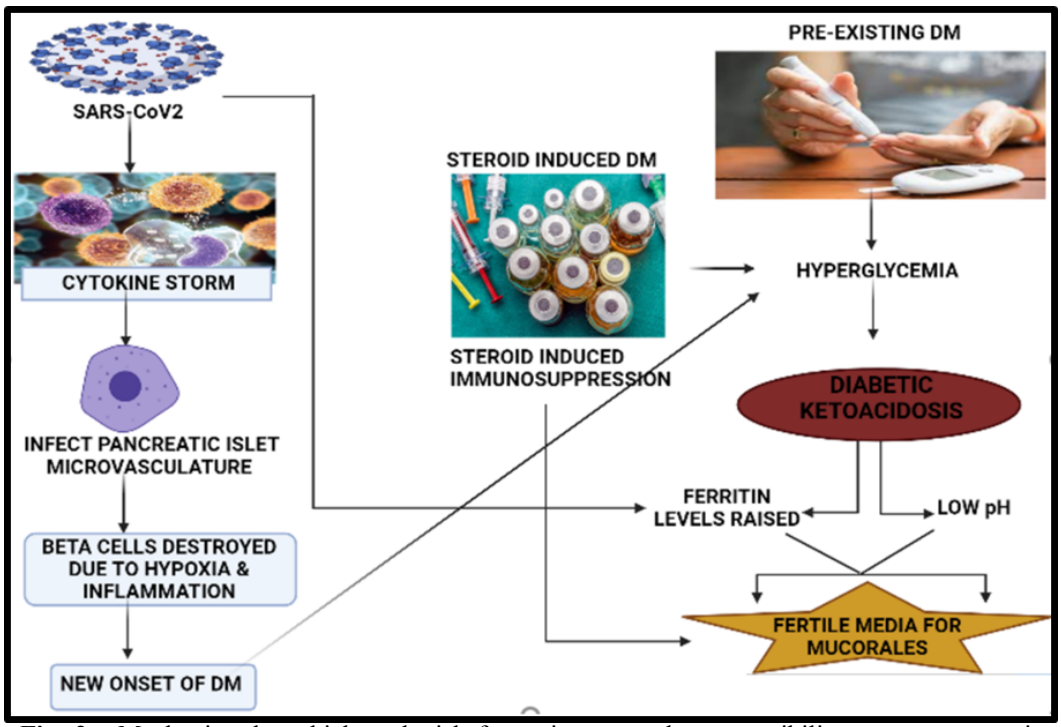

Fig. 2 - Mechanism by which each risk factor increases the susceptibility to mucormycosis (Tamez-Pérez et al., 2015; Prakash et al., 2019; Singh et al., 2021; Revannavar et al., 2021).

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8. Diagnosis

The most crucial element in the treatment of mucormycosis is the diagnosis, because the longer it takes to detect the disease, the higher the probability of death. Histological analysis confirms the diagnosis, which is then verified by a culture test (Fig. 3). Based on the symptoms and indicators listed in Table 1, the presence of mucormycosis has been verified. Because the number of mucormycosis patients is expected to increase during COVID-19, a medical team should be on hand to provide immediate access to imaging instruments as well as histological and mycological research. Diabetic patients with sinusitis or pneumonia-like symptoms should be evaluated immediately, and diabetic patients on dialysis are at risk of mucormycosis and should be treated as high-risk patients. COVID-19 patients on steroid medication should also be monitored carefully.

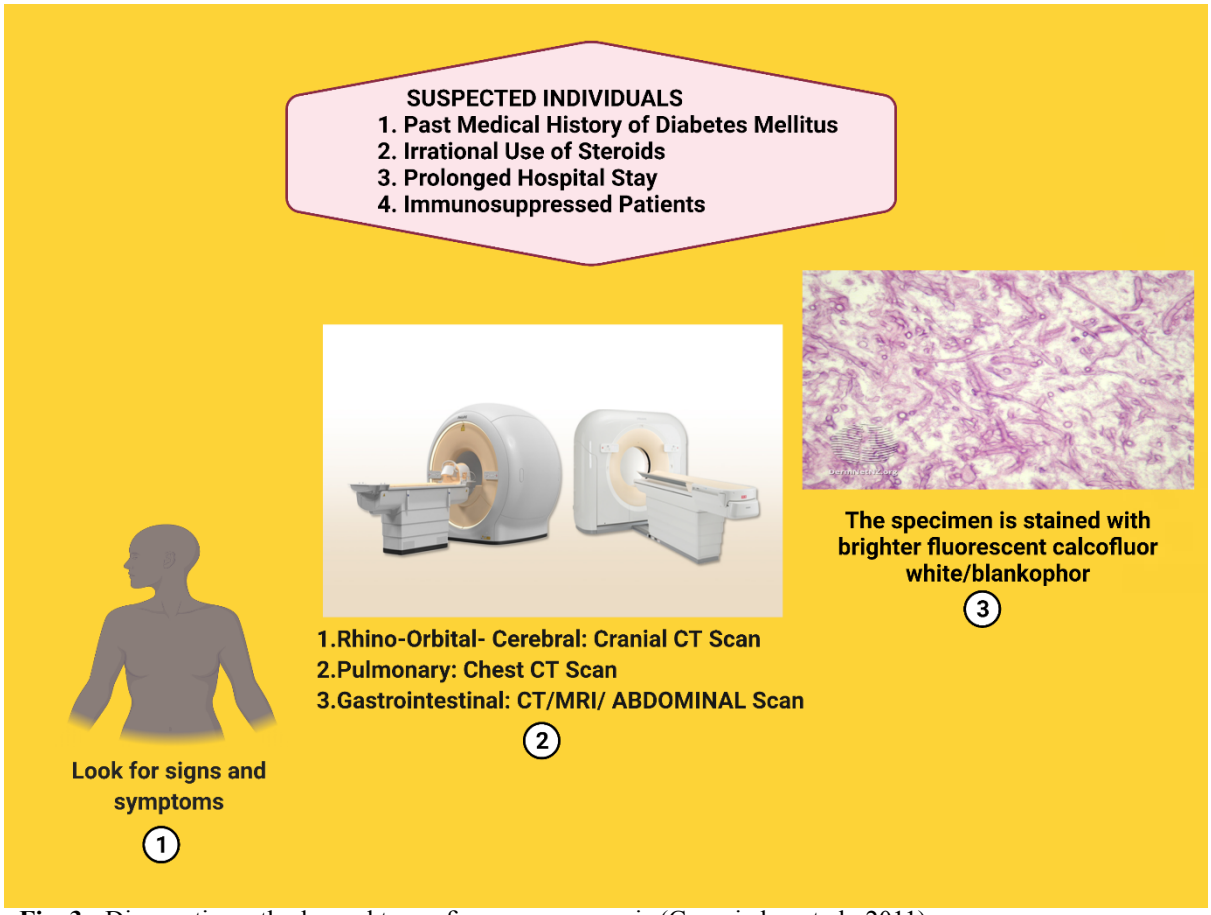

Fig. 3 - Diagnostic methods used to confirm mucormycosis (Georgiadou et al., 2011).

The following are some indications of mucormycosis that can be seen on a CT scan (Georgiadou et al., 2011).

- Halo sign
- Reverse halo sign
- Vessel occlusion in pulmonary angiography

If orbital involvement is suspected, a Magnetic Resonance Imaging (MRI) should be performed after a CT scan to determine the extent of the infracted area/necrotized tissue (Cornely et al., 2019).

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9. Management

By July 19th, a minimum of 11 different Indian-specific treatment guidance for COVID-19 Associated Mucormycosis (CAM) were available (Aranjani et al., 2021). In general, most of the national guidelines warn to optimize missing corticosteroids use and control diabetes along with immediate and extensive radiology-guided surgical intervention as treatment choice (Aranjani et al., 2021). Most commonly followed was 2019 global guidance on mucormycosis by the European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium (Cornely et al., 2019) and Code Mucor was considered compendious among them, with a treatment algorithm that suits every substage (Honavar, 2021). In general, most national guidelines warn about controlling diabetes and optimizing corticosteroids use. Immediate and extensive radiology-guided surgical intervention was the treatment of choice.

The India-centric guideline by ECMM and the International Society for Human and Animal Mycology (ISHAM) for stage 4 disease, recommends extensive debridement of external infected tissues, including bones and repeated procedures in case of recurrence (Rudramurthy et al., 2021). All the guideline recommends the use of systemic antifungal agents without any prophylactic therapy. The Indian Council of Medical Research (ICMR) (ICMR, 2021) recommends administering antifungal therapy for at least 4 to 6 weeks and liposomal amphotericin B (AmB, 5 mg kg^{-1} per day) with slow infusion. Dose escalation up to 10 mg kg^{-1} per day is recommended if the infection spreads to the CNS (DGHS, 2021). Azoles (Isavuconazole or posaconazole) are suggestive if AmB is contraindicated. The Fungal Infection Study Forum and ECMM/ISHAM recommends itraconazole when AmB or the primary azoles are unavailable (Rudramurthy et al., 2021; FISFTRUST, 2021).

Given the risk of fatality, a clinical choice about how to proceed following the diagnosis should be made as soon as possible. In general, mucormycosis in COVID-19 is treated with a combination of surgical and antifungal therapies (CDC, 2022). It's also critical to pinpoint the patient's trigger element and eliminate it. For best results, the debridement technique should be repeated as needed (Skiada et al., 2018). Modifications can be made depending on the availability of the medications listed in the Figure 4 (Cornely et al., 2019).

10. Recommendations based on ICMR guidelines

The ICMR recommendation **(**Tamez-Pérez et al., 2015) has been amended to lower the risk of mucormycosis, according to the present situation.

- It's important to keep your blood glucose levels in check
- Monitor the chances of hyperglycemia during post-COVID-19 as there is a risk for new onset of diabetes Mellitus and pre-existing diabetes
- Steroids should be administered cautiously with short course **(**5-10 days) and low doses in COVID-19 patients with continuous blood glucose monitoring and should be avoided at the occurrence of mucormycosis.
- Use humidifiers while on oxygen supplementation
- Keep an eye out for signs and symptoms of mucormycosis while in the hospital
- Rapid surgical intervention along with antifungal therapy has to be immediately administered

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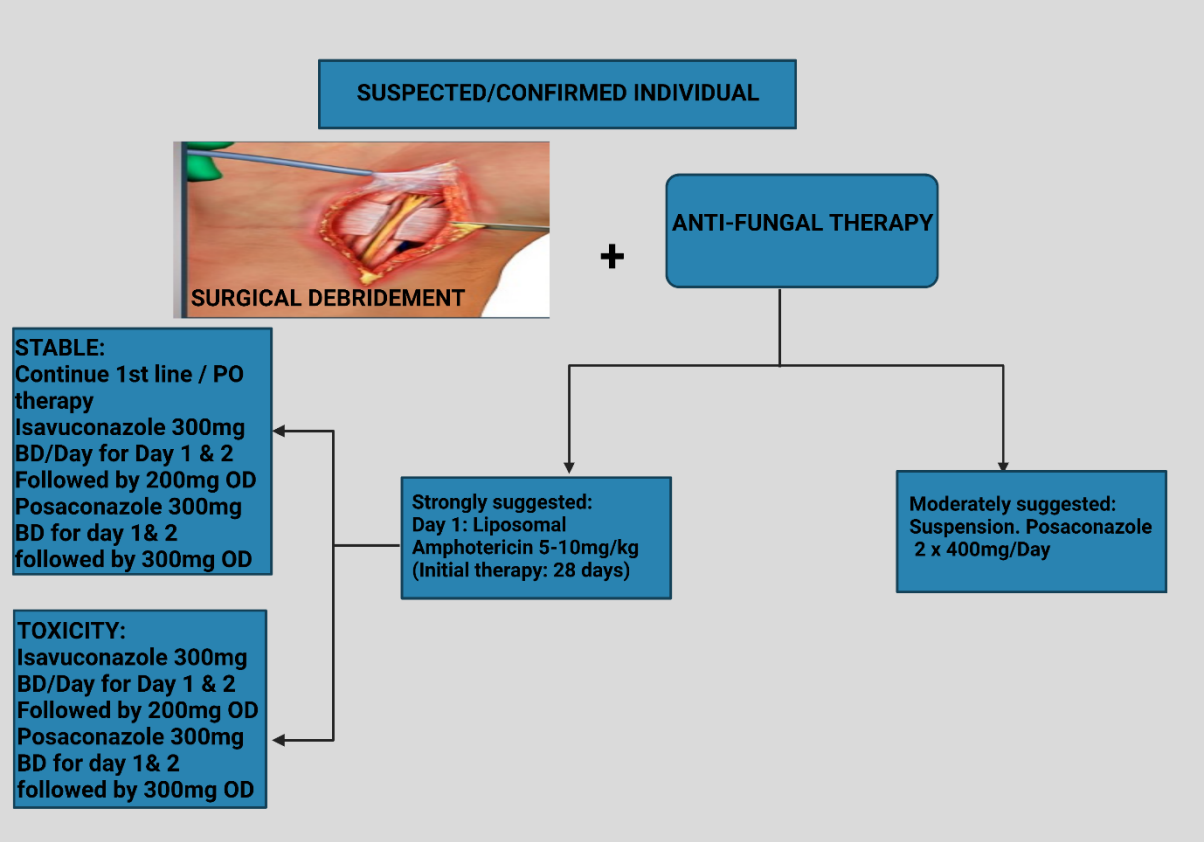

Fig. 4 - Anti-fungal therapy to be given for mucormycosis (Cornely et al., 2019).

11. Understanding the cases reported in India and other countries

Diabetes mellitus and steroid medication, as previously stated, are the most common risk factors among the cases documented. Various published case reports (Supplementary Table 1) showed that steroid medication can raise blood sugar levels and hence needs to be under control. The majority of the patients were in a critical condition requiring mechanical ventilation, necessitating a prolonged stay in the hospital.

12. Further research

More research is needed to determine whether mechanical ventilation increases the risk of mucormycosis. The risk of lung damage after mechanical breathing has already been discussed (Ragaller and Richter, 2010). Mechanical ventilation is considered to increase inflammatory response and, as a result, threat to patient which is shown in Figure 5.

13. Conclusion

In light of the current situation in India, it is critical to address this life-threatening fungal infection. Mucormycosis prevalence and mortality is very high in Indian COVID-19 patients related to non-judicious steroid use, high incidence of diabetes mellitus, delays in seeking treatment and diagnosing and challenges in managing advanced disease condition. It is necessary to pre-empt the risk factors of Mucormycosis case by case to curtail the outbreaks. Although the impact of mechanical ventilation-

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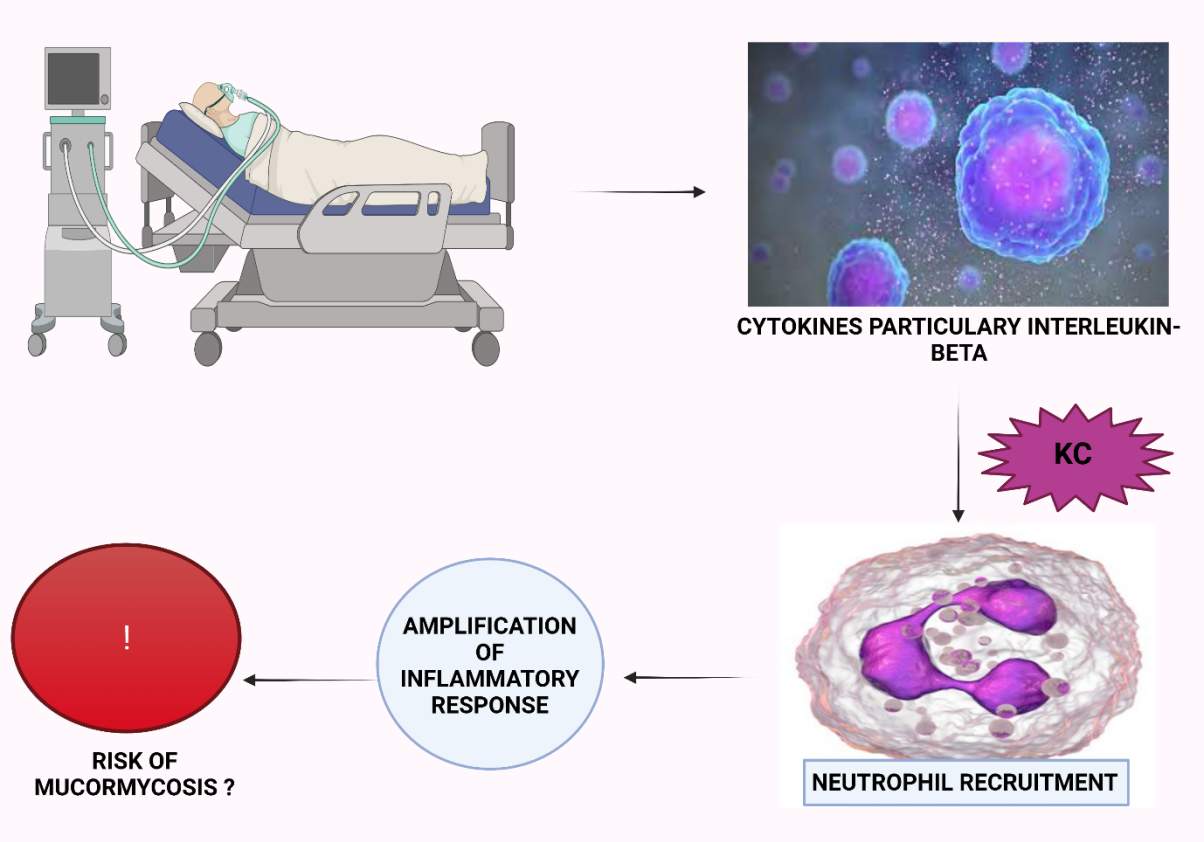

Fig. 5 - Can mechanical ventilation increase the risk of Mucormycosis in COVID-19? (KF = Kupffer Cells).

induced mucormycosis remains unproven, careful monitoring need to be done and this study also emphasizes the need of early diagnosis of the disease for reducing mortality. Lowering the severity of COVID-19 and reducing the length of hospital stay is utmost important to minimize the hospital-acquired mucormycosis. Some recommendations to make during COVID-19 management include judicious use of steroids, hyperglycemia management, and lowering the severity of COVID-19, extensive debridement of external infected tissues and bones in severe cases, administering liposomal amphotericin B (AmB) as first-line therapy and Azoles a second-line therapy if AmB contraindicated.

Ethical Considerations

This is a review article and the Institutional ethical committee has confirmed that no ethical approval is required.

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

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