

## Decode: COVID-19 Associated Mucormycosis

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### Abstract

### Original Research Article

The coronavirus infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be related with a wide range of disease and ranging from mild to life-threatening pneumonia. Patients with COVID-19 have higher susceptibility to fungal coinfections. Mucormycosis is a rare and-threatening fungal infection. Mucormycosis is more common in immunocompromised individuals, and patients with uncontrolled diabetes. COVID-19 associated mucormycosis usually developed 10-14 days after hospitalization. A high number of suspicion diagnosis and aggressive management is required to improve outcomes of the therapy. Awareness of warning symptoms and signs play an important role for the identification of the mucormycosis.

**Keyword:** COVID-19, Mucormycosis, Immunocompromised, life-threatening, diabetes.

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## INTRODUCTION

The corona virus disease (COVID-19) has spread rapidly on a global scale it is caused by novel Corona virus SARS-CoV-2. The mortality rate is high due to severe pneumonia caused by SARS-CoV-2. Secondary infection due to bacteria and fungi is also common in COVID -19 patents that increase the mortality rate.(1,2,40) In COVID-19 patients the transmission and diffusion of oxygen is impaired due to the malfunctioning and distraction of endothelial barrier [3] profound lymphopenia may alter the immune response in COVID-19 patients and increase the risk of fungal infection [4].

COVID -19 patients suffering from Acute respiratory distress syndrome for the reason of that they required long term stay in intensive care unit (ICU) and mechanical ventilation and also treated with high dose of corticosteroid all these factor increases risk to develop fungal infection like mucormycosis [5-8]. Corona virus disease affects T-helper cells which can increase the risk of confections in COVID -19 patients [9, 10]. Mucormycosis is life treating fungal infection caused by few genera of fungi in order Mucorales [11].

Rhizopus arrhizus is the most species in India .Mucorales are thermo-tolerant fungi .they are found on

organic substrate such as decaying vegetables and fruit, animal excreta, indoor and outdoor soil and Mucorales are also present in indoor environments such as air conditioning filters air conditioning filter [12-15].

The agents of mucormycosis are incapable of penetrating into intact skin. But several condition like, burns and traumatic disruption of the skin condition the organism to penetrate into deeper tissues [16].

Mucormycosis infection may develop several weeks after recovery from COVID 19. Patients with moderate to severe COVID-19 is very susceptible to mucormycosis due to decrease CD4+ and CD8+lymphocytes [17].

## METHODS

Literature search was performed in Pub Med for English-language studies published from June 2021 through 31 July, 2020. Review, original article, Case report, Editorial, Article, multicenter study, research article, clinical investigation were included in this review We also manually searched the references of selected articles. Selected articles were mutually agreed by the authors.

### Risk factor

Individuals who lack phagocytes or have impaired phagocytic function are at higher risk of mucormycosis [16]. The most common risk factor associated with mucormycosis is diabetes mellitus in India [11]. The most common risk factors of mucormycosis is generally observed in patients with uncontrolled diabetes mellitus with ketoacidosis, and lung disease or having immunosuppressive therapy, conditions such as patients receiving cancer chemotherapy, corticosteroid treatment, or immunotherapy, haematological stem cell transplants, those with prolonged neutropenia stem cell and solid organ transplants or Iron chelating therapy [11, 18].

Acute diabetes and diabetic ketoacidosis can be inducing by SARS-CoV-2 by damaging pancreatic islets cells [19-21]. Iron and hyperferritinaemia, Iron overload and deferoxamine therapy are well known risk factors for mucormycosis [22]. Secondary fungal infection is more common in sever ill hospitalized COVID -19 patients .The usages of corticosteroid in the treatment of COVID -19 may increases the risk of further fungal infection [5].

Corticosteroids reduced the activity of immune system as well as it also causes drug induced hyperglycemia both of provoke the clinical therapy of the patients. For diabetes patients corticosteroid immediately discontinued from the therapy and elevated level of blood glucose level controlled with insulin therapy [23].

### Clinical features

Symptoms like nasal blockage and discharge, headache, pain and redness around eyes or nose, fever, coughing, shortness of breath, hematemesis, Mucormycosis may affect the lungs [2]. But nose and sinuses are the most frequent infection sites. It can then spread to the the brain, causing headaches and seizures and also to the eyes, causing blindness [24]. A trademark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessel thrombosis, infarction and tissue necrosis [25].

### Pathogenesis

The fungal spores implant usually entry into the host body through fungal spores in the oral, nasal and conjunctival mucosa (rhino-orbito-cerebral), by inhalation (pulmonary), or by the ingestion of contaminated food (digestive) they used glucose as a main energy source and rapidly colonize in host body [19]. They have affinity for arteries and grow along internal elastic lamina causing infarction thrombosis [19, 26] individuals who lack phagocytes or have impaired phagocytic function are at higher risk of mucormycosis.

### Role of diabetes in mucormycosis

Uncontrolled diabetes plays an important role in pathogenesis of mucormycosis. SARA-CoV-2 itself causing diabetes and diabetes ketoacidosis by the damaging pancreatic islets cells and indirectly by damaging small blood vessel of pancreatic beta cells [27, 28]. Profound inflammatory reaction in COVID -19 patients increase resistance to insulin and may increase blood glucose level [29].

Type2 diabetes mellitus itself is an immunocompromised state which makes the host susceptible to mucormycosis infection. Hyperglycemia and acidosis can induce phagocyte cell dysfunction it may leads increased risk of Mucorales infections [16, 30].

### Role of Corticosteroids' in mucormycosis

The use of corticosteroids in the treatment of COVID-19 play a important role in pathogenesis of mucormycosis.corticosteroid can increase blood glucose level, it act as a substrate for oxidative stress metabolism. it also increase insulin resistance in patients [22] corticosteroid also affect the immune response by affecting immune cells, they antagonized the i) suppression of microbicidal activity of activated macrophages ii) decrease of interleukin-1, interleukin-6, proinflammatory prostaglandins and leukotrienes production by macrophages and tumour necrosis factor, iii) antagonism of macrophage maturation and differentiation [31].

### Role of Iron and hyperferritinaemia in mucormycosis

Hyperferritinaemia condition is developing in severe COVID-19 patients due to hyper inflammatory state [32]. Excess iron in the body increases the risk off mucormycosis because free iron captured by the *Rhizopus* species and helps it in the growth [33]. Excess intracellular iron generated reactive oxygen species (ROS) causing damage to the tissue [34].

### Diagnosis

Early diagnosis of Mucormycosis can reduce the mortality and morbidity of the infection clinical microbiological, histopathological and radiological parameter is help for the successful management of the disease [3, 4, 35].

A patient who has Sign and symptoms of Mucormycosis (Nasal stuffiness ,Facial pain, Proptosis, sudden loss of vision, facial edema, mucoid, blood tinged or black nasal discharge ), recently (<6weeks) treated COVID-19, use systemic corticosteroid , use supplement oxygen or patient on mechanical ventilation is considered as possible suspect for Mucormycosis. Microbiological, histopathological, molecular and radiological parameter is help for the diagnosis of Mucormycosis. Suspected patients diagnosed by nasal endoscopy, MRI and CT scan, direct microscopy or

histopathology. Mucormycosis is diagnosed by regular investigation of blood glucose level, ferritin level [35].

Real-time fluorescence (RT-PCR) has been the current standard diagnostic method for diagnosis of COVID-19, by detecting the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and secretions of the lower respiratory tract samples [36, 37, 38].

The prognosis of mucormycosis is poor. Diagnosis of mucormycosis is very difficult. Early intimation of the treatment is very important element for the therapy it decrease the mortality rate [39].

### Treatment

The management of mucormycosis in COVID-19 patients are similar to the management of Mucormycosis in non -COVID-19 patients. (35) Treatment of Mucormycosis carried out by two way Medical treatments with Antifungal drug therapy and surgical debridement.

### Antifungal drug therapy

Amphotericin B is a fungistatic drug rather than fungicidal, which leads to required longer duration for the treatment. Hyperbaric oxygen therapy and local treatment with Amphotericin B are adjuvant procedure [40].

Amphotericin B (lipid based formulation) is used as a drug of choice for the first line therapy for the treatment of mucormycosis. Liposomal Amphotericin B is strongly recommended at a dose 5mg/kg per day in 200ml of 5% dextrose over 2-3h for 3-6 weeks. Posaconazole and isavuconazole use as alternative at the place of Amphotericin B [41].

### Surgical Management

Surgical debridement is the most difficult decision in mucormycosis treatment due to concerns about disability and disfigurement but it can be life-

saving [40]. Surgical removal of necrotic tissue, debridement, and enucleating of the eye if involved, has also proved to be lifesaving [12, 40]. A combined medical and surgical management used for the better survival in Mucormycosis therapy [42]. Liposomal amphotericin B is the first-line therapy for the treatment of mucormycosis along with surgery (if possible) [43].

### Prevention

The incidence of mucormycosis in COVID-19 patients may be reduced by optimizing the use of systemic Corticosteroids, by the monitoring and control of Diabetes mellitus, maintain proper hygienic condition, sterile water used for the humidifier for those who has on oxygen support, mask used for covering of face and nose, or by minimizing the patients exposure to the potential source of infection.

Oral Posaconazole are used as a prophylactic treatment For the high risk patients like those patients who receiving COVID-19 treatment with mechanical ventilation, used supplement oxygen or used systemic corticosteroid, for more than three week uncontrolled diabetes mellitus with or without ketoacidosis, or receiving immune suppression drug [35].

Other clinical interventions include proper cleaning and sterilization of humidifiers and ventilators, utilization of disposable or disinfected personal protective Equipment and proper hygiene maintenance. Important factors such as steroid monitoring control of blood sugar level, and dosage variance according to the severity of COVID-19 infection. Inappropriate steroid consumption raises the blood sugar level and weakens the immune system, a condition that favors fungal infection. Medical procedures include rapid control of diabetic ketoacidosis, reduction or discontinuation of steroids and immunomodulating drugs, antifungal prophylaxis, radio imaging and clinical monitoring of fungal progression [39] Table 1.

**Table-1: Prevention of mucormycosis in the COVID-19 Patients**

Sensible and supervised use of systemic corticosteroids.
Regularly and invasive monitoring of diabetes mellitus.
Maintain blood sugar level.
Daily change, Use sterile water for the humidifier and maintain aseptic condition for oxygen support patient.
Maintain Personal and environmental hygiene.
Betadine mouth gargle used regularly.
Use masks covering the nose and mouth.
For the prophylactic oral Posaconazole use in high-risk patients (>3 weeks of mechanical ventilation, >3 weeks of supplemental oxygen, >3 weeks of systemic corticosteroids, uncontrolled diabetes mellitus with or without ketoacidosis, prior history of chronic sinusitis, and Co-morbidities with immunosuppressant).

## CONCLUSION

Early diagnosis is important for better result of Mucormycosis patients. During discharging from the COVID ward all those patients especially diabetic and under ICU or taking corticosteroid during the treatment of COVID therapy should be advised to take list of sign

and symptoms of Mucormycosis. Physician should be aware about mucormycosis especially during the first to second week after COVID 19 in immunocompromised and diabetic patients. Awareness of warning symptoms and signs play a important role for the identification of the mucormycosis and clinical suspicion patients early

diagnosis by a diagnostic nasal endoscopy and direct microscopy of the high nasal swab or an endoscopically guided nasal swab, supported by contrast-enhanced MRI or CT scan without wasting time. Initiation full-dose liposomal Amphotericin B used as first line drug therapy for the management of the disease. Clinical suspicion and early treatment with surgical debridement are key to preventing mortality and morbidity.

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