Review Article

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Unravelling the Knots between Uncontrolled Diabetes, Corticosteroids and SARS-CoV-2 in the Rising Incidence of "Deadlier" Mucormycosis

Sonal Jain

Abstract

The second wave of COVID-19 in early 2021 has caused havoc across the globe and despite a bit flattening curve of SARS-CoV-2 cases in India, another fatal complication known as CAM created chaos in the whole country. An alarmingly high increase in the number of cases led to the healthcare infrastructure inadequacy due to excessive demand for hospital beds, drugs, oxygen, and vaccines. The rhino-orbital-cerebral form is the most common clinical presentation observed. A complex interplay between uncontrolled blood glucose, unjudicial use of corticosteroids and SARS-CoV-2 infection has to an upsurge in CAM cases. The majority of these cases had diabetes as predisposing comorbidity and corticosteroids were administered to treat COVID-19. Probable pathologic mechanisms may involve immunological and inflammatory processes. Diabetes, together with COVID-19 induces systemic immunological alterations, leading to decreased immunity and an augmented risk of secondary infections. Prolonged use of high-dose corticosteroids acts as another risk factor for CAM. The hypoxic conditions in COVID-19, uncontrolled diabetes, steroid-induced hyperglycemia, DKA, and increased ferritin levels due to SARS-CoV-2 mediated immunosuppression provide a perfect environment for the Mucorales spores germination in these patients. The recommended treatment strategies mainly include surgical debridement and antifungal therapy using Amphotericin B and selected azoles. Several clinical guidelines focusing on Indian patients have been proposed for accurate diagnosis of infection, identifying clinical presentation, understanding the pathogenesis mechanisms, and tracking the disease course for rapid management of the disease.

Keywords: COVID-19 associated mucormycosis; Corticosteroids; Diabetic ketoacidosis; Diabetes mellitus; Ferritin; Rhino-orbital-cerebral mucormycosis.

Author's Affiliation: Senior Consultant, Medical Affairs (Content and Communications), Mumbai, Maharashtra 400051, India.

Corresponding Author: Sonal Jain, Senior Consultant, Medical Affairs (Content and Communications), Mumbai, Maharashtra 400051, India.

E-mail: Sjain.77@rediffmail.com
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Introduction

India has been one of the most impacted countries in the world with the second wave of COVID-19. According to the recent estimates, the number of cases reached a maximum number of somewhat greater than 4 lakhs on May 7, 2021, and a decline was observed after that. Despite a reduction in the number of new cases, India still accounted for around 34% of the deaths worldwide during the third week of May 2021.[1]

Despite that further worsening of the SARS-CoV-2 infection has not been observed, and the infection curve is a bit flattened in India, another danger which India has confronted is in the form of COVID-19 Associated Mucormycosis (CAM). Mucormycosis (MCR) is a rare but life-threatening fungal disease caused by Mucorales fungi (*Rhizopus oryzae, Rhizomucor pusillus, Apophysomyces variabilis and Lichtheimia corymbifera*). The threat is bursting at alarming rates throughout India and raising

health concerns across the globe. This rare, but life-threatening fungal infection has accounted for 41,512 cases and 3,554 fatalities from May 5-July 12, 2021. The Central Government of India has declared a mucormycosis epidemic on May 10, 2021, owing to the preponderance of cases that occurred during active SARS-CoV-2 outbreaks in India.[2]

The rhino-orbital-cerebral mucormycosis (ROCM) is the most common type of mucormycosis which occurs when the vulnerable hosts inhale the spores into the paranasal sinuses.[3,4] The angioinvasion and vascular thrombosis results in tissue necrosis, often as a late symptom, and is considered as the hallmark of mucormycosis infection. The global case fatality of mucormycosis is 46%.[3] The co-morbidities such as poorly controlled type 2 diabetes mellitus (DM), hypertension and other cardiac diseases act as independent risk factors for both severe COVID-19 and MCR.[5]

Another critical factor playing role in the emerging cases of mucormycosis is the unjustified use of corticosteroids to treat severe/critical SARS-CoV-2 infection.[5] The second wave of COVID-19 has resulted in an abrupt increase in the incidence of mucormycosis in India, with a minimum of 14,872 reported cases on May 28, 2021.[6]

Uncontrolled Diabetes as an Independent Risk Factor for COVID-19 Associated Rhino-orbital-cerebral Mucormycosis (ROCM)

Pathophysiology of Rhino-orbital-cerebral Mucormycosis (ROCM)

Uncontrolled diabetes mellitus and the immunocompromised state of an individual are major risk factors for the rare but fatal rhino-orbital-cerebral mucormycosis (ROCM) fungal infection. Roughly 70% of the cases demonstrate diabetic ketoacidosis (DKA) events. The nose and paranasal sinuses are often origin points of the clinical condition but subsequently, the infection spreads to the orbital areas also. The pathogenesis includes the destruction of the adjacent bone and soft tissue due to vascular thrombosis leading to tissue infarction by the infiltrating fungus; this can involve the brain later which can have fatal complications.[7] The corticosteroids cause immunosuppression which together with diabetic microangiopathy and peripheral microthrombi in COVID-19 creates an ideal environment for mucormycosis progression.[3]

In the hyperglycemic state, several mechanisms can alter the normal immunologic response of the body to the infection such as stimulation of fungal propagation, decrease in chemotaxis and phagocytic efficiency, facilitating the fungus to flourish in an acid-rich environment. There is an increased risk of mucormycosis in DKA patients caused by *Rhizopus oryzae* because of the production of the ketoreductase enzyme in these organisms, enabling them to consume the patient's ketone bodies.[7] The hypoxic conditions in COVID-19, uncontrolled diabetes, steroid-induced hyperglycemia, metabolic acidosis, DKA,

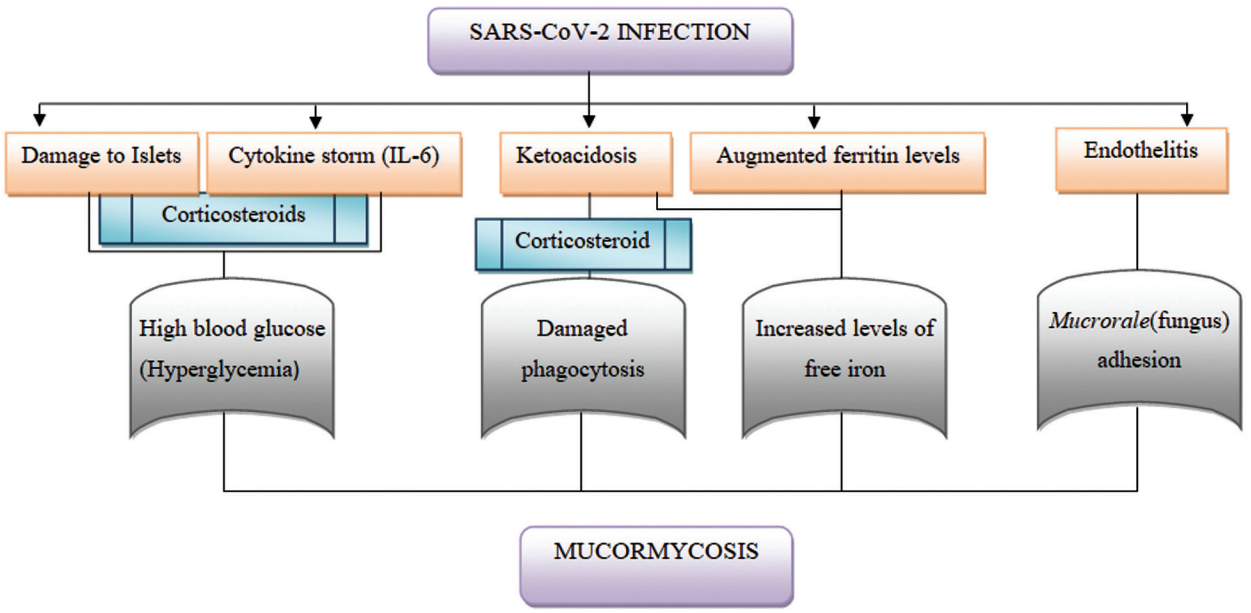

Fig. 1: Probable causative mechanisms for Mucormycosis in SARS-CoV-2 infection[8] (Adapted from Pal R et al. Mycoses. 2021; 00:1–8).

augmented ferritin levels and reduced phagocytic activity of white blood cells (WBC) due to SARS-CoV-2 mediated immunosuppression provide a perfect locale for the Mucorales spores to germinate in people with COVID-19 (Fig. 1).[8]

Even though both innate and adaptive immune responses get stimulated as a result of fungal invasion into the host tissues but hyperglycemia causes a fault in the innate immune system which consequently leads to decreased phagocytosis and inhibits neutrophil migration and chemotaxis. DKA increases the likelihood of developing mucormycosis by 50% than without DKA and ROCM is generally always associated with DKA. Furthermore, ketone bodies (beta-hydroxybutyrate) increase the availability of free iron due to their high pH. This high pH and increased availability of free iron create an ideal zone for fungal growth in a vulnerable host. The expression of GRP78 (Glucose Regulator Protein 78) in endothelium and fungal spore coating protein family (CotH3) is also increased at a physiological concentration of ketone bodies.[9]

Hyperglycemia can also increase the risk of mucormycosis by several other mechanisms even if DKA is not present. These include: (i) weakens phagocytosis and chemotaxis by neutrophils, (ii) blockade of the action of iron sequestrating proteins, (iii) increase of GRP78 and CotH3 fungal protein (iv) by impairing the oxidative and nonoxidative pathways.[9]

Moreover, clinical studies have also demonstrated that besides poor glycemic control, the management requires extremely high doses of insulin in COVID-19 patients. The probable explanation for transitory elevated glucose levels is connected to insulin resistance due to the upregulation of inflammatory cytokines during infection.[10]

Exploring the correlation between uncontrolled diabetes and mucormycosis in SARS-CoV-2 infection: Evidence-based insights

As the cases of mucormycosis showed a steep rise, which necessitated clinicians and researchers to dig deep for associated pathogenetic mechanisms and risk factors. Worldwide, several systematic reviews and observational studies have been conducted since then that have established that poor glycemic control acts as an independent risk factor for the development of mucormycosis in COVID-19 infection.

The majority of the evidence-based data revealed that a remarkably high proportion of patients with clinical presentation of mucormycosis included in the research studies had uncontrolled DM.

In a literature review conducted between December 2019–April 2021, on a total of 41 mucormycosis cases (83% (N=34) males with a median age of 55 years) obtained from individual case reports or case series, the glycemic condition was available for 35 cases and 94% of these cases (33/35) had DM with a mean glycosylated hemoglobin (HbA1c) of 10%. Moreover, 71% (29/41) of the cases were reported from India. A total of 44% (8/18) of the DM patients had diabetic ketoacidosis (DKA). The clinical presentation was rhino-orbital and ROCM which is distinctive of MCR seen in diabetic patients. These results point that DM acts as a risk factor for MCR in COVID-19 patients with high morbidity and mortality. The patients with COVID-19 are prone to DKA similar to the other severe infections[5] and SARS CoV causes acute diabetes and DKA by damaging pancreatic islets.[9] There occurs a down-regulation of angiotensin-converting enzyme 2 (ACE 2) receptors in pancreatic islets, together with increased insulin resistance owing to cytokine storm leading to what is called as the "diabetogenic state" in SARS-CoV-2 infection. Consequently, intensification of the *ACE (Angiotensin converting enzyme) → Angiotensin II→AT1 receptor axis* with the considerable weakening of *ACE→Angiotensin II→Mas receptor axis* is observed.[11]

Similarly, a retrospective, interventional institutional cohort study conducted at Regional Institute of Ophthalmology, Ahmedabad, Gujarat, India from September 2020 to mid-March 2021 on a total of 31 patients (mean age 56.3 years) with biopsy-proven mucormycosis established a correlation between uncontrolled DM and rhino-orbital mucormycosis in COVID-19 patients. Overall, 96.7% (N=30/31patients had DM with 61.2% COVID-19 positivity (N=19/31). Uncontrolled type II DM was seen in 93.5% of patients (N=29/31), and one patient had uncontrolled type I DM (N=1/31). The average HbA1c level observed was 7.57mmol/mol. The commonest clinical presentation was a diminution of vision (<6/60) in 80.64% of patients followed by ophthalmoplegia in 77.4% of patients. Other forms of clinical presentations were intracranial extension in the form of cerebral involvement, internal carotid artery thrombosis, and cavernous sinus thrombosis in 22.58%, 6.45% and 3.22% of patients, respectively. Only three deaths were observed of which only one, a 71-year-old diabetic male with positive COVID-19 history showed ROCM as clinical presentation. The main cause of death was

DKA with multiple organ failure. The presence of cerebral involvement and a HbA1c level of ≥8 mmol/mol were found to be significant predictors of 75-day mortality *(P≤ 0.05)*.[12]

Another systematic literature search of case reports/case series across the globe and in India was conducted in the electronic database of PubMed and Google Scholar from start until May 13, 2021. The articles were searched for confirmed and suspected cases of mucormycosis and a total of 101 cases of mucormycosis (95 confirmed and 6 suspected) in people with confirmed (RT-PCR diagnosis) COVID-19 were extracted. The majority of cases were reported from India (81.2%) with only 18.8% of cases from other parts of the world (8.9% from the USA and 3.1% from Iran and roughly 7% from the rest of the world). The pooled data analysis revealed a preponderance of the male gender with mucormycosis (78.9%), both in active (59.4%) or recovered (40.6%) COVID-19 patients. Hyperglycemia either due to pre-existing DM or new-onset hyperglycemia or DKA was the solitary most important risk factor in the majority of cases (83.3%) of mucormycosis in COVID-19 patients. Further, pre-existing DM constituted for 80% of cases, while associated DKA accounted for approximately 15% of patients with mucormycosis and COVID-19. The nose and sinus involvement was observed in maximum cases (88.9%), followed by rhino-orbital mucormycosis (56.7%) and ROCM type (22.2%). On the whole, mortality was noted in 30.7% of the cases.[13]

In another recent systematic review, using PubMed, Scopus and Google Scholar databases till 14 May 2021 and conducted on a total of 30 case reports/case series, pooling data retrieved from 99 patients with CAM again revealed DM as a major risk factor for mucormycosis. The majority of the cases were reported from India (72%) with male gender preponderance (78%) and DM (85%). A previous history of SARS-CoV-2 infection was present in 37% of patients with mucormycosis and the symptoms developed after an initial recovery. A median time interval of 15 days was observed between COVID-19 diagnosis and the first evidence of mucormycosis infection or CAM diagnosis. Rhino-orbital mucormycosis was most common (42%), followed by ROCM (24%). The mortality rate was 34% and adjunct surgery was associated with better clinical outcomes (P <0 .001).[8]

The findings of the Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1 Indian study were consistent with all the previously discussed studies. It was a retrospective, observational study conducted on 2826 patients in India from January 1, 2020 to May 26, 2021 and DM was reported to be a major risk factor in COVID-19 associated ROCM. The mean age of patients was 51.9 years and 71% were males; DM was present in 78% of all patients. Most of the cases (56%) showed onset of symptoms of ROCM within 14 days after COVID-19 diagnosis, where as 44% showed delayed onset beyond 14 days. The orbit involvement was seen in 72% of patients, with stage 3c (bilateral orbit involvement) constituting the (27%).[14]

Unjudicial Use of Corticosteroids is An Important Predisposing Risk Factor in the Development of COVID-19 Associated Mucormycosis (CAM).

Corticosteroid Use and Pathogenesis of Mucormycosis: What's the link?

Another critical risk factor predisposing COVID-19 patients to mucormycosis infections and worsening of hyperglycemia is the inappropriate use of systemic corticosteroids and antiviral agents for the treatment of COVID-19. An increased incidence of mucormycosis infections has been observed in COVID-19 patients administered with corticosteroids during treatment.[2] Corticosteroids and immunosuppressive agents act as risk factors and prolonged high dose of corticosteroids augments the risk to angioinvasive mucormycosis infection. Corticosteroid intake often leads to uncontrolled hyperglycemia and precipitation of DKA. Low pH due to acidosis in DKA acts as a fertile environment for Mucorales spore germination (Fig. 2). Other mechanisms of pathogenesis due to steroid use include:

1. Reduction in the phagocytic activity of WBC.[13]
2. Damage to bronchoalveolar macrophages migration, ingestion, and phagolysosome fusion.[13]

Do Corticosteroids Augment Risk of CAM?: Evidence-based insights

One classical example is the rampant use of the parenteral dexamethasone (a glucocorticoid) which has been reported as a major risk factor for the development of mucormycosis. Glucocorticoid-induced immunosuppression, hyperglycemia and lymphopenia are contributing factors in the pathogenesis of mucormycosis. A systematic review conducted on 30 case reports/ case series has reported that in 85% of CAM cases, glucocorticoid was administered for the

management of COVID-19.[8] Similar findings have been reported in several other studies wherein the use of corticosteroids for the management of COVID-19 was observed in 88% cases (N=41)[5], 76. 3% cases (N=101)[13], and 61.2% cases (N=31)[12], respectively where N is the total number of patients.

In the COSMIC study, 87% of the patients were treated with systemic corticosteroids either oral and/or intravenous (IV) of which 21% were administered for more than 10 days. A total of 78% received IV corticosteroids; the common ones were methylprednisolone (51%) and dexamethasone (48%) for a median duration of six days. Oral corticosteroids were administered in 64% for a median duration of eight days. The use of corticosteroids was directly correlated with an increased proportion to the severity of COVID-19. Among 2029 patients who were hospitalized, a high proportion of patients were administered with corticosteroids; 80% of those who did not require oxygen, 93% of those who required oxygen by prongs/mask, 99% of those who required high-pressure non-invasive ventilation, and 97% of those on mechanical ventilation. Amongst non-diabetic patients, 89% received corticosteroids. One interesting finding of this study was that even though 43% of patients did not require oxygen support during the treatment of COVID-19 but a majority of them had DM and received corticosteroids indicating that contaminated oxygen might not be the impelling factor for infection.[14]

The use of high-dose corticosteroids in patients with COVID-19 disease necessitates assessment. One study showed that sticking to the use of low-dose corticosteroid (methylprednisolone in a dose of 1 mg/kg/day not more than 40 mg twice a day for a maximum of 3 days) and good glycemic control (blood glucose level between 140 and 180 mg/dl through the admission in the intensive care unit (ICU) followed along with minimum use of other immunomodulatory drugs such as monoclonal antibodies) were critical factors in contracting no mucormycosis infection among 1027 ICU patients regardless that 40% had DM and corticosteroids were used in 89% of these patients.[16]

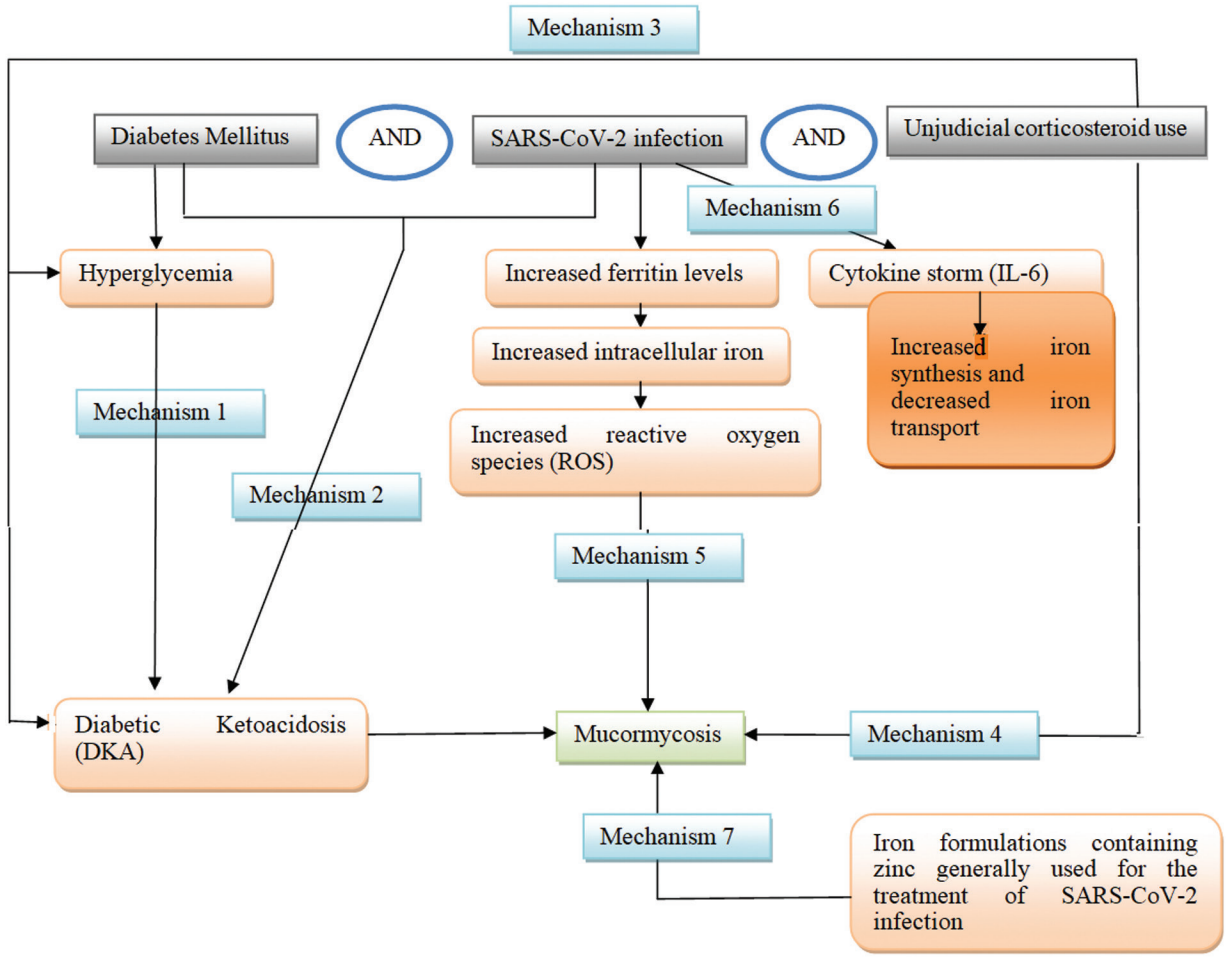

Fig. 2: Complex inter-relationships between hyperglycemia and unjudicial steroid use in the pathogenesis of mucormycosis in COVID-19.[15]

The Viral Modulation of Iron Homeostasis and Iron Overload

The modulation of iron homeostasis and claiming of host iron is one of the most important virulent characters of Mucorales. *Invitro* studies have demonstrated a direct correlation between the growth curve of *Rhizopus* and the availability of free iron in the serum.[8] The poor growth of R. *oryzae* in iron-deficient medium explains the importance of iron in the growth and metabolism of Mucorales.[13] Therefore, in humans, the sequestration of serum iron by its binding to iron storage proteins like transferrin and ferritin thus making free iron unavailable to pathogens, constitutes an important defense mechanism against Mucorales.[8]

Dysregulation of iron homeostasis and iron overload is a prominent factor in the pathogenesis of SARS-CoV-2.[13] During active infection, there occurs an interaction between the viral particle and hemoglobin molecule through the angiotensin converting enzyme 2(ACE2) and CD147 receptors leading to viral endocytosis through the spike protein(a protein on the viral surface SARS-CoV-2).[17] Consequently, this enables a cascade of events causing dysfunctional hemoglobin, hemolysis, accumulation of heme and reduced oxygen transportation. Hyperferritinemia (increased serum ferritin) occurs due to macrophage activation and increased Interleukin-6 (IL-6) secretion which is a clinical marker of acute inflammation. Ferritin is responsible for iron storage, thereby protecting the cells from excessive free iron and its toxic effects.[18] Furthermore, this excessive free iron leads to oxidative stress [production of reactive oxygen species (ROS)] and lipoperoxidation of cell membranes.[17]

This ROS-mediated endothelial damage catalyzed by the available free iron and ferritin leads to diffuse inflammation of endothelium called 'Endothelitis'.[17,19] The existing condition deteriorates in a complex mechanism including the hepcidin mimetic effects of SARS-CoV-2 by using its spike proteins to invade the cytoplasm. This causes the dysregulation of iron metabolism following hyperferritinemia and ferroptosis.[20]

Key recommendations from National and International Guidelines for the Antifungal Therapy in the Management of CAM in India.[18, 21-27]

Guideline	Antifungal treatment for CAM
AIIMS[21]	• Amphotericin B • Posaconazole
CIDS[22]	Amphotericin-B deoxycholate » 1 mg/kg/day IV, 4–6 weeks Liposomal Amphotericin B » 5 mg/kg/day IV, 4–6 weeks Isavuconazole IV/oral » 200 mg three times a day for 2 days » Followed by 200 mg once daily, 4–6 weeks Posaconazole IV/Tab » 300 mg two times a day for 1day » Followed by 300 mg once daily, 4–6 weeks
DGHS–India[23]	Liposomal Amphotericin-B » 5 mg/kg body weight » High dose (10 mg/kg), if the CNS is involved **Step down therapy:** Posaconazole oral, delayed-release » 300 mg two times a day for day 1 » Followed by 300 mg daily Isavuconazole oral » 200 mg three times a day for 2 days » Followed by 200 mg daily
ECMM/ ISHAM[18]	**First-line treatment** » Liposomal Amphotericin B(strongly recommended) » 5 mg/kg/day in 200 ml 5% dextrose; 2–3 hours infusion for 3–6 weeks **Azoles, posaconazole and isavuconazole are effective** Consider itraconazole ***only*** if other treatments are unavailable » 200 mg/kg/day for 3–6 weeks » To be considered in patients with diabetes » Avoid in case of haematological malignancy
FISF[24]	**Liposomal Amphotericin-B(preferred)** » 5 mg/kg/day in 200 cc 5% dextrose; 2–3 hours infusion » 10 mg/kg/day (a high dosage), if the brain isinvolved **Amphotericin B deoxycholate** • 1 mg/kg/day in 5% dextrose; 6–8 hours infusion **Alternative agents for the patients intolerant to Amphotericin B** • Posaconazole tablet » 300 mg two times a day for the first and second day » Followed by 300 mg once daily • Isavuconazole tablet » 200 mg thrice daily for 2 days » Followed by 200 mg once a day If polyene or the 2 azoles are not available then Itraconazole » 200 mg three times a day for 3–6 weeks with food » Order of dosage form preference: injection, suspension, tablet

ICMR[25]	• Amphotericin B infusion (infuse with normal saline IV before drug infusion) • Antifungal therapy for a minimum of 4–6 weeks.
IMA[26]	**First-line treatment** **Liposomal Amphotericin-B (preferred)** » 5 mg/kg/day in 200 cc 5% dextrose; 2–3 hours infusion. » 7.5–10 mg/kg/day (a high dosage), if brain isinvolved. **Injection Amphotericin-B Deoxycholate** » 1 mg/kg/day in 5% dextrose; 6–8 hours infusion. » **Premedication to avoid infusion reaction:** Nonsteroidal anti-inflammatory drugs and/or diphenhydramine or acetaminophen with diphenhydramine or hydrocortisone, normal saline pre-infusion (500–1,000 ml). **Injection Amphotericin-B Lipid Complex** » 5 mg/kg/day **Second-line treatment: Azoles** **Posaconazole delayed-release tablet** » 300 mg twice daily on day 1 » Followed by 300 mg once daily with food **Isavuconazole tablet** » 200 mg thrice daily on days 1 and 2 » Followed by 200 mg once a day
WHO, South-East Asia: India[27]	• Liposomal Amphotericin-B (preferred) • **Azoles**: Posaconazole and Isavuconazole
Code Mucor[28]	**Immediate induction therapy** **Liposomal Amphotericin B (5–10 mg/kg body weight) with strict metabolic control** **On contraindication of Amphotericin B:** • **Isavuconazole IV.** » 200 mg three times a day for the first 2 days » 200 mg once daily from day 3 • **Posaconazole IV** » 300 mg two times a day on day 1 » 300 mg once daily from day 2 **Continue induction therapy for at least 4 weeks** • **IV Amphotericin B (5–10 mg/kg body weight)** • **Step down therapy for 3–6 months:** • Isavuconazole oral » 200 mg three times a day for the first 2 days » 200 mg once daily from day 3 • **Posaconazole oral** » 300 mg two times a day on day 1 » 300 mg once daily from day 2

Surgical Treatment: The majority of the Guidelines recommend surgical debridement (including extensive surgical debridement also).

AIIMS: All India Institute of Medical Sciences; **CIDS:** Clinical Infectious Disease Society; **CNS:** Central Nervous System; **DGHS:** Directorate General of Health Services; **ECMM/ISHAM:** European Confederation of Medical Mycology and the International Society for Human and Animal Mycology; **FISF:** Fungal Infection Study Forum; **ICMR:** Indian Council for Medical Research; **IMA:** Indian Medical Association; **IV:** Intravenous; **WHO:** World Health Organization.

Conclusion

CAM has emerged as an alarming threat to the human species worldwide with India being the locus of this fatal disease. The triage of uncontrolled type 2 DM, unjudicious use of corticosteroids and SARS-CoV-2 has resulted in the rising incidence of mucormycosis disease. The Indian Council of Medical Research (ICMR) has issued guidelines for the screening, diagnosis, and management of mucormycosis in patients with SARS-CoV-2 infection. Several Indian states have implemented treatment strategies for the disease rapidly and Liposomal Amphotericin B in an initial dose of 5mg/kg body weight (10 mg/kg body wt in case of CNS involvement) is the treatment of choice.[29]

The use of corticosteroids based on 3 R's (at Right time with Right dose and for Right duration) and the monitoring of blood glucose levels are the key fundamentals to minimize the incidence of CAM cases. The use of steroids is not advised in asymptomatic and mild COVID-19 cases. Moreover, self-medication with steroids must be avoided.[29]

The future of the pandemic and CAM depends on how precisely the managements goals are designed and achieved across the globe. A continuous and stepwise approach must be taken by all the medical organizations throughout the world and in India to combat the pandemic to bring normalcy to human lives again.

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