COVID-19–associated mucormycosis (CAM)

October 2021
- **Mucormycosis** is an uncommon, life-threatening infection caused by filamentous fungi of the order *Mucorales* and class *Zygomycetes*. These ubiquitous organisms can be found in bread mold, soil, manure, and decaying vegetation.

- Mucormycosis is one of the primarily opportunistic invasive mycoses that frequently develop in immunocompromised patients who have received hematopoietic stem cell or solid organ transplantations or who have hematologic malignancies.

- Moreover, mucormycosis can occur in immunocompetent patients with diabetes mellitus, subcutaneous tissue injury, and iron overload.
✓ Uncontrolled DM
✓ Iron overload or hemochromatosis
✓ Severe burn
✓ AIDS
✓ Intravenous drug abusers
✓ Trauma
✓ Prolonged neutropenia
✓ Corticosteroid therapy
✓ Hematological malignancies
✓ Transplantation
In the mid-20th century, diabetes evolved as a major risk factor for mucormycosis, while in more recent years, underlying malignancy emerged as another important risk factor due to the increasing number of patients undergoing chemotherapy or cancer immunotherapy.

With more solid organ and HSCT being performed, increasing numbers of cases have also been reported in these patient groups.
COVID-19–associated mucormycosis (CAM)

- Coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with a wide range of opportunistic bacterial and also fungal infections.

- Both *Aspergillus* and *Mucorales* have been reported as the main fungal pathogens for co-infection in people with COVID-19. Several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide.
Mucormycosis did not draw similar attention, as the disease was considered rare. Recent reviews on worldwide cases highlighted the importance of COVID-19– associated mucormycosis (CAM) globally.

Distribution of different species causing mucormycosis varies amongst different geographical regions.
Mechanism of increased propensity of having mucormycosis infection in COVID-19 patients

The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 are:

- Ideal environment of hypoxia
- Cytokine release during COVID-19, High cytokines (IL6), higher disease severity
- Endothelial cell dysfunction
- Hyperglycemia (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia)
- Acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA])
- High iron levels (increased ferritins)
- Decreased phagocytic activity of white blood cells due to immunosuppression SARS-CoV-2 mediated, steroid-mediated or background comorbidities
- Several other shared risk factors including prolonged hospitalization with or without mechanical ventilators
Uncontrolled diabetes in CAM

- Among COVID-19 patients, uncontrolled diabetes had been reported at 7%–21%. Acute or stress-induced hyperglycemia has been noted in 50% of hospitalized COVID-19 patients.

- SARS-CoV-2 itself can induce acute diabetes and diabetic ketoacidosis by damaging pancreatic islets cells, which have a high expression of angiotensin converting enzyme-2 receptors, as has been noted with SARS-CoV-1, and indirectly by damaging small blood vessels supplying pancreatic beta cells.

- Increased resistance to insulin due to the profound inflammatory reaction, may also play some role in the induction of hyperglycemia.

- Hyperglycemia and acidosis can induce phagocytic cell dysfunction leading to increased risk of Mucorales infections.
Endothelial damage

- SARS-CoV-2 infection alters the integrity of vessel barrier, lead to endothelitis and subsequent alternation in homeostasis and perfect vascular function. Also virus attaching to the endothelia cells and abnormal increase in cytokines such as IL-1, IL-6, IL-8, and TNF-α, can alter the blood coagulation factors including d-dimer and fibrinogen and hence leading to venous thrombosis and endothelial cell apoptosis and injury.

- Endothelia cell damage in the context of cytokine release in SARS-COV-2 and exposed the extracellular matrix proteins can direct interaction with Rhizopus spores. Subsequently these spores adhere and invades endothelial cells with this special attachment.
Corticosteroids

- **CS-induced hyperglycemia** in these patients is one of the predisposing factors of mucormycosis and can help in the rapid proliferation and growth of this fungal hyphae.

- Also doses of CS with immunosuppression effect, which suppresses the function of immune cells such as macrophages, neutrophils and T cells and thus, with the suppression of immune, make individuals susceptible to fungal infections.
Iron and hyperferritinaemia

- **Cytokine release** cause ferritin as an inflammatory markers increased. In this situation Iron can not bind to ferritin and the level of free iron increases. These free iron induces functional defect in neutrophil and T lymphocytes.

- Mucorales have high affinity iron permease that transport and utilize the iron in the host cell. High iron concentration due to inflammation causes reactive oxygen species (ROS) production and further tissue damage occur.
High IL-6 concentrations in COVID-19 patients have been correlated to disease severity.

IL-6 directly stimulates ferritin production and increases the synthesis of hepcidin which in turn sequesters iron in enterocytes and macrophages thus preventing them to efflux from these cells leading to increased intracellular iron load.
SARS-CoV-2

- Heart
- Lungs
- Blood Vessels

Respiratory & Circulatory Disturbance/Failure

- SaO₂ ↓

Hypoxia

- Innate Immune Cells
- Cell Death
- DAMPs
- HIF-1α Transcription ↑
- Cytokines ↑

- Macrophages
- Neutrophils

- VEGF ↑
- Integrins ↑
- Vascular Permeability ↑

- SDG ↑
- ROS ↑
- NETs ↑

COVID-19 ARDS, Pneumonia
Fig. 1. Postulated interaction of diabetes, corticosteroid and COVID-19 with mucormycosis.
Clinical Presentation

- During the present epidemic nearly 90% of cases presented as Rhino-orbito-cerebral mucormycosis (ROCM) and <10% as pulmonary or disseminated disease.

- Cutaneous mucormycosis is rarely reported in SARS-CoV-2 infected patients.
When to suspect COVID-19 associated ROCM?

- Any patient, either in the acute phase of COVID-19 or in the post-COVID-19 phase, presenting with visual deterioration, Periorbital swelling, proptosis, facial pain or numbness, headache, nasal obstruction or nasal bleed must be dealt with a high index of suspicion.

- Neurological manifestations in the form of encephalopathy, focal neurological deficit or seizures may also be seen.
Diagnosis

- Early diagnosis of mucormycosis is of importance, since it may improve outcome. Studies have shown that it increases survival.

- Diagnosis consists of recognition of risk factors, assessment of clinical manifestations, early use of imaging modalities and prompt initiation of diagnostic methods based on histopathology, cultures and advanced molecular techniques.

- Patients with suspected mucormycosis should be referred immediately to a facility with the highest care level.
What investigations help in the diagnosis and management of ROCM?

- Craniofacial imaging plays an important role in the early diagnosis, staging and follow up of patients with ROCM.

- CT may show a mucosal sinonasal thickening with absence of fluid levels and hyperdense content leading to erosions/remodelling of bony sinus walls.

- Because of a superior resolution, MRI provides a better visualization of the involved orbital soft tissue, infra-temporal fossa, intracranial structures, perineural invasion and vascular compression or obstruction.
Histopathological examination

- Histopathologically, *Mucorales* hyphae have a variable width of 6–16 μm, but may be up to 25 μm, and are non-septate or pauci-septate. In tissue, the hyphae appear ribbon-like with an irregular pattern of branching.

- Demonstration of this kind of hyphae and isolation of *Mucorales* from endoscopically collected debrided tissue/biopsy or a CT guided biopsy from a lung lesion confirms the diagnosis of mucormycosis.
Treatment approaches for CAM

- Standard approaches for the management of CAM are similar to the management of mucormycosis in non-COVID-19.
- Timely initiation of an effective antifungal therapy along with aggressive surgical debridement of necrotic lesions; reverse of immunosuppression and when feasible control of the underlying medical condition are necessary.
- **Surgical resection of necrotic tissues is the core of mucormycosis therapy.**
First-line antifungal monotherapy

- In general, primary antifungal therapy for mucormycosis should be based on a polyene, if possible.

- Although amphotericin B deoxycholate (AmB) was the cornerstone of mucormycosis therapy for decades, lipid formulations of AmB are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time than AmB.

- **First-line treatment with liposomal amphotericin B (5–10 mg/kg per day) is strongly supported across all patterns of organ involvement.**

- Use of amphotericin B deoxycholate should be restricted to settings in which there is no other antifungal therapy available.
New triazoles

- Triazoles act by depleting ergosterol from the fungal cell membrane. Among Triazoles antifungals, fluconazole, itraconazole, and voriconazole have little or no activity against *Mucorales*.
- Newer Triazoles, namely posaconazole and isavuconazole, have better in vitro activity against *Mucorales* and clinical data supporting their use in mucormycosis.
- **Salvage treatment** may be necessary because of refractoriness of disease, or because of intolerance towards previous antifungal therapy, or because of a combination of both.
- **Isavuconazole** is strongly supported as salvage treatment.
- **Posaconazole delayed release tablets OR infusions** are supported for salvage treatment, and when available should be preferred over posaconazole oral suspension, which in turn is marginally supported for salvage treatment.
- Recently isavuconazole have been studied as first-line therapy for mucormycosis.
- Posaconazole has been mainly studied as salvage therapy and could be an option as salvage therapy in patients unresponsive or intolerant to LAMB.
Posaconazole

To overcome the pharmacokinetic limitations of the oral solution a gastro-resistant tablet and an intravenous (IV) solution has been developed.

The advantages of the tablet formulation over the suspension include better bioavailability allowing once-daily dosage, no food requirements, absorption unaffected by changes in gastric pH or motility; and more predictable plasma concentrations than the suspension.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Indications</th>
<th>Dosage and delivery</th>
<th>Side effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphotericin B</strong></td>
<td>Initial therapy</td>
<td>- 1-1.5 mg/kg/d IV</td>
<td>- Infusion reactions</td>
<td>Liposomal AmB is drug of choice, if available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 5-10 mg/kg/d IV</td>
<td>- Phlebitis</td>
<td>Therapeutic drug monitoring not required</td>
</tr>
<tr>
<td></td>
<td>- AmB-deoxycholate</td>
<td>- 5-10 mg/kg/d IV</td>
<td>- Acute Kidney Injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Liposomal AmB</td>
<td></td>
<td>- Hypokalaemia, hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- AmB Lipid Complex</td>
<td></td>
<td>- Anaemia</td>
<td></td>
</tr>
<tr>
<td><strong>Posaconazole</strong></td>
<td>Step down or</td>
<td>- IV: 300 mg BD on 1st day then 300 mg OD</td>
<td>- Nausea, vomiting, Diarrhoea</td>
<td>Erratic absorption warrants use of therapeutic drug monitoring</td>
</tr>
<tr>
<td></td>
<td>Salvage therapy</td>
<td>- Oral suspension: 200 mg 6 hourly</td>
<td>- Headache</td>
<td>Drug interactions high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>followed by 400 mg BD after stabilization of disease</td>
<td>- QTc prolongation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tablet: 300 mg BD 1st day followed by 300 mg OD</td>
<td>- Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Oedema</td>
<td></td>
</tr>
<tr>
<td><strong>Isavuconazole</strong></td>
<td>Step down or</td>
<td>- IV: 372 mg every 8 h for 6 doses then 372 mg once a day</td>
<td>Nausea, vomiting, diarrhoea, headache QTc prolongation, hepatic toxicity, oedema and hypokalaemia</td>
<td>Therapeutic drug monitoring not required</td>
</tr>
<tr>
<td></td>
<td>salvage therapy</td>
<td>- Oral: 372 mg every 8 h for 6 doses</td>
<td></td>
<td>Fewer drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>then 372 mg once a day</td>
<td></td>
<td>Isavuconazone sulfate (IS) is prodrug of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isavuconazole (372 mg of IS is equivalent to 200 mg of Isavuconazole)</td>
</tr>
</tbody>
</table>

AmB-Amphotericin B, IV-Intravenous.
There are no definitive data to guide the use of antifungal combination therapy.

Limited data support combinations of polyenes and azoles or polyenes plus echinocandins.

Combination therapy can be rationally given due to lack of enhanced toxicity with possible but unproven benefit; however, data are too limited to support this beyond a marginal recommendation.
Treatment duration for mucormycosis

- There is no standard duration of treatment for mucormycosis. Decisions are made on an individual basis, and as a principle, antifungal therapy of mucormycosis is continued until resolution of all clinical, laboratory, and imaging signs and symptoms of infection and reversal of immunosuppression.

- Oral formulations of newer azoles with activity against *Mucorales*, such as posaconazole and isavuconazole have an important role in bridging the initial IV treatment of mucormycosis to long-term treatment.

- Posaconazole oral suspension can be used, but is marginally supported, especially when formulations with higher exposure are available.
Thank You
For Your Attention