

COVID-19 Associated Mucormycosis (CAM)

Dr Nasirmohtaram

Otorhinolaryngologist, Head & Neck Surgeon

Assistant Professor of GUMS

CAM

- Risk factors
- Timing of occurrence
- Symptoms and signs and sites
- management

Epidemiology

- Globally, the highest number of cases has been reported in India,
- More than 47000 cases were reported in 3 months
- Important due to high mortality rate, sheer number of patients and shortage of anti fungal agents
- The current epidemiological situation incorporates patients with COVID-19 into the list of risk factors of mucormycosis

epidemiology

- Mucormycosis has always interested the medical community, given the fulminant course and devastating effect on the host
- Most reported cases were from India, then the rest of the world (most commonly from Iran, followed by the US)

epidemiology

- The reasons for this surge of mucormycosis cases remain unknown.
- The 'epidemiologic triad' (environment, agent, and host factors) is a practical model to explain the occurrence of a new disease or a reemerging disease

Environmental factors

- Despite the fungi being ubiquitous, mucormycosis is mostly encountered as an opportunistic infection in an immune-compromised host
- Outbreaks of cutaneous infection by Mucorales have been reported from hospitals associated with **contaminated** adhesive bandages, linen, and wooden tongue depressors

Environmental factors

- Less frequently, rhino-orbital or pulmonary mucormycosis has been encountered after exposure to **contaminated air** (from ongoing construction, contaminated air conditioners, or ventilating systems)
- In this pandemic, acute shortage of oxygen and hospital beds led to **unhygienic delivery of oxygen** including use of industrial oxygen, prolonged use of humidifiers without cleaning and unmonitored use of oxygen delivery
- In a study from India, approximately 9% of the mucormycosis (primarily cutaneous) cases were nosocomial

environmental

- Some experts believed that wearing **face masks** over a long time without washing them might have some role in CAM pathogenesis, though extensive research is needed in this aspect.??
- ✓ Tropical weather?
- ✓ construction activities in the hospital setting can make the fungal spores airborne?

Agent factors

- The etiologic agent responsible for mucormycosis is a group of thermotolerant eukaryotic fungi of the order Mucorales. The order Mucorales comprises 261 species in 55 genera, at least 38 of which have been associated with human infections
- The fungal sporangiospores enter the human body mainly by **inhalation** and less commonly by **ingestion** or **direct inoculation**. The large spores (e.g., *Rhizopus arrhizus*) commonly settle in the upper respiratory tract, while the smaller spores (for instance, *Cunninghamella*) reach the lower respiratory tract

Agent factors

- While Mucorales usually do not cause infection in healthy individuals, the capacity of polymorphonuclear leucocytes may be overwhelmed when the **hyphal load** is high.
- Certain Mucorales such as **Cunninghamella** are known to be highly virulent and proliferate rapidly

Agent factors

- SARS-CoV-2 is constantly undergoing genetic mutations and variations, whereas the genetic makeup of fungi is **generally stable**.
- However, fungi may also acquire **virulence factors** over time
- Notably, a recent study had reported microevolution in *Cryptococcus neoformans* (both in vivo and in vitro), causing hypervirulence

Agent factors

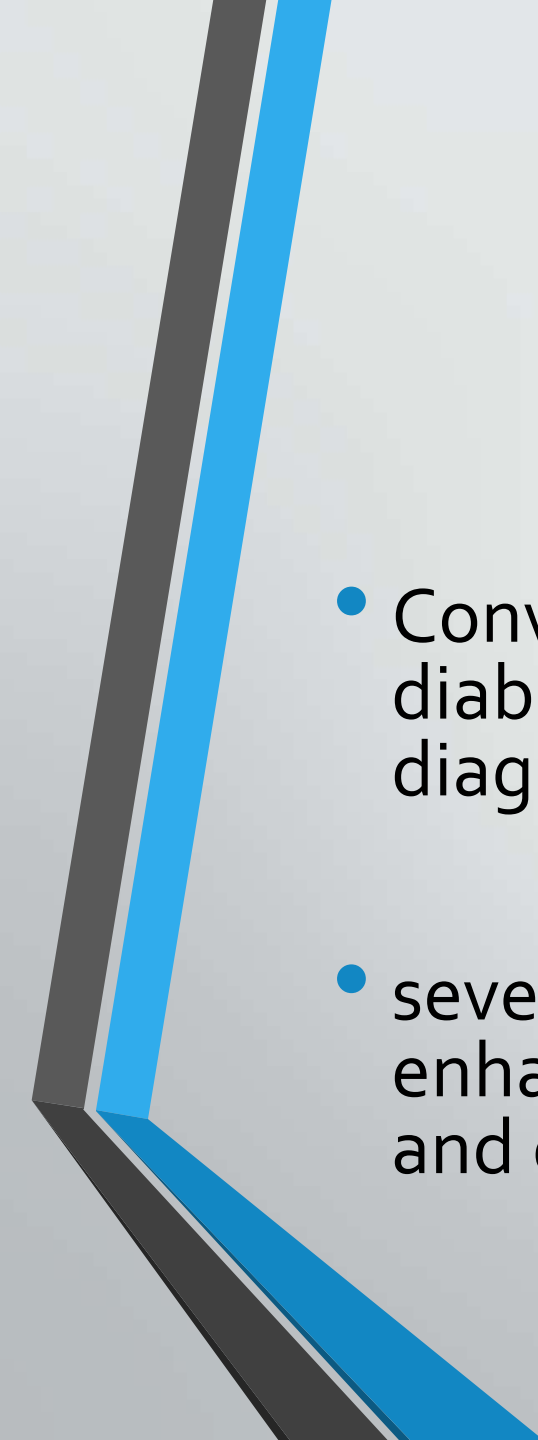
- Whether the Mucorales have acquired hypervirulence factors contributing to the current epidemic needs to be studied.
- Additionally, the role of SARS-CoV-2 in modulating the interaction between Mucorales and the human host is also not known

Host factors

- Innate immunity is primarily responsible for clearing the spores from mucosal surfaces in healthy individuals.
- **Neutrophilic disorders** (qualitative or quantitative) are the main risk factors for mucormycosis, while lymphocytic disorders have rarely been implicated as a predisposing factor for mucormycosis

Diabetes mellitus

- Diabetes mellitus is a risk factor for severe COVID-19 and is associated with increased mortality due to COVID-19.
- Diabetes impairs **innate** immune function by impairing phagocytic function, which significantly improves following glycemic control.
- Further, impaired dendritic cell responses delay the timely activation of **adaptive** immune responses.

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- Conversely, COVID-19 can lead to the **onset of diabetes**, and diabetic ketoacidosis (DKA) has been precipitated in newly diagnosed diabetes following COVID-19s
 - severe COVID-19 increases **insulin resistance** through enhanced secretion of stress hormones (cortisol and others) and cytokines

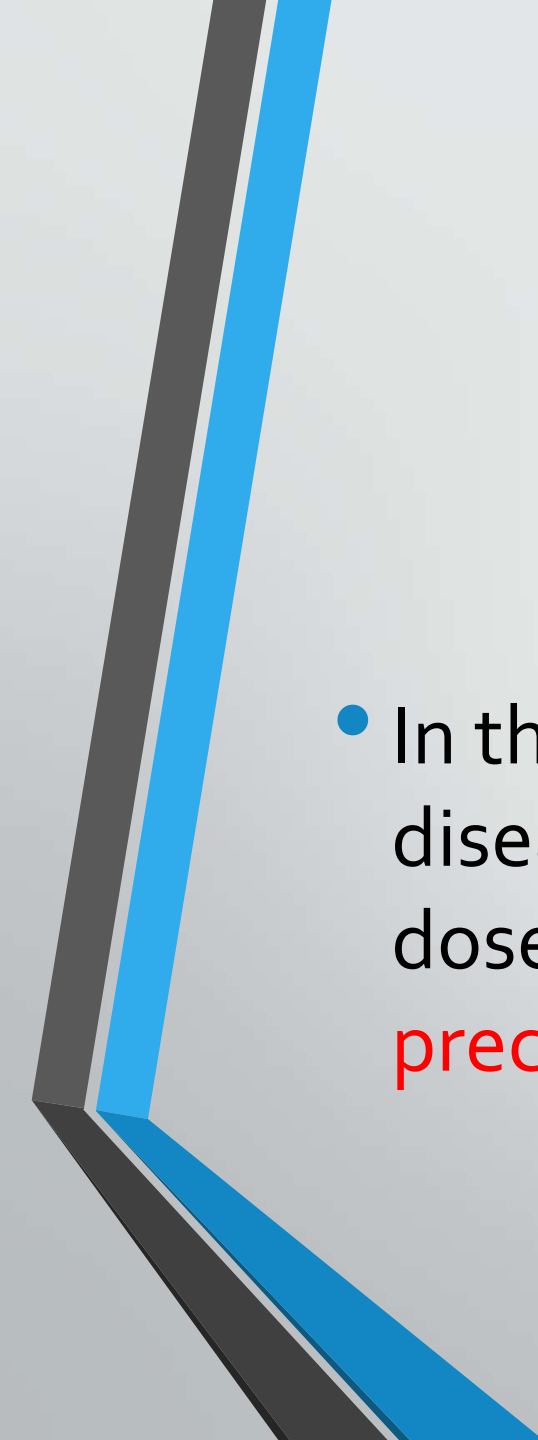
Iron Metabolism

- Hyperferritinemia, due to the profound inflammation, is a characteristic feature of COVID-19 and is associated with increased mortality.
- Notably, ferritin-associated iron induces defects in innate (neutrophils) and adaptive immunity (T-lymphocytes) in mice models
- Interestingly, the acquisition of iron from the host is essential for the growth of Mucorales

- Patients with **iron overload** are more prone to mucormycosis , especially those receiving the iron chelator deferoxamine
- In patients with **DKA**, acidosis temporarily dislocates iron bound to transferrin . The ketoacid, b-hydroxybutyrate, indirectly compromises the ability of transferrin to chelate iron. The increased iron can permit the growth of R. arrhizus
- multivitamins supplementation including zinc and iron ???

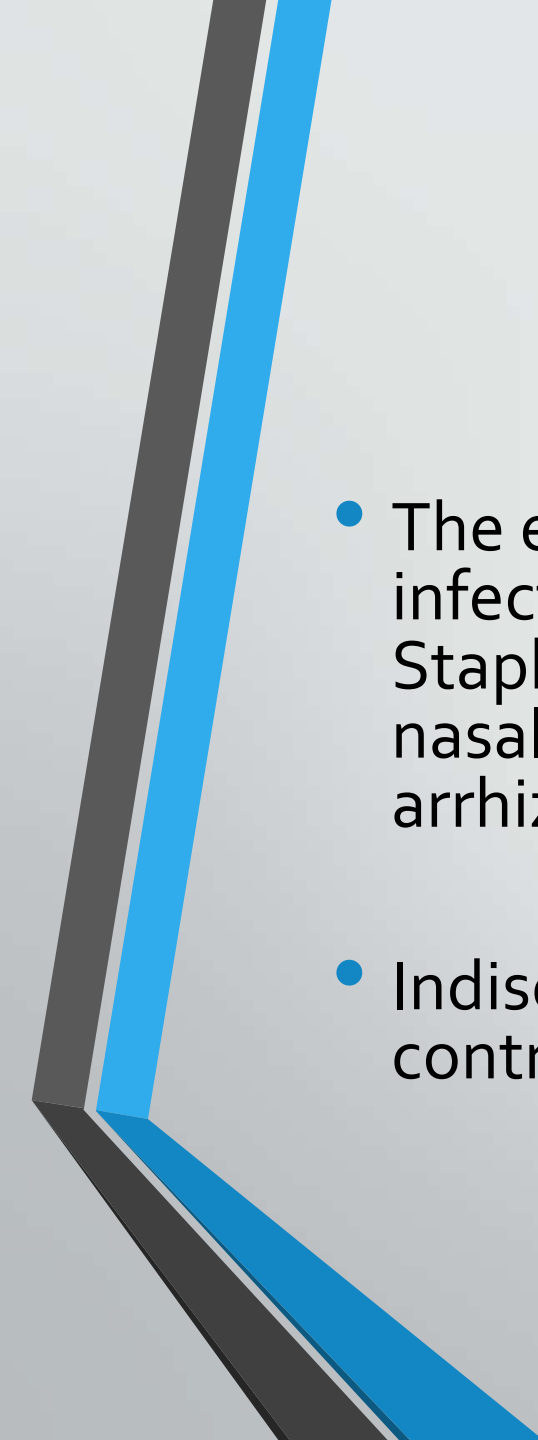
Glucocorticoids


- Corticosteroids are an important predisposing factor for CAM. They are potent **immunosuppressants** with a wide range of effects on various aspects of adaptive and innate immunity
- Apart from the effects of chronic hyperglycemia on phagocyte and neutrophil functions, even short-term glucocorticoids can precipitate **hyperglycemia** and have been shown to predispose to mucormycosis .
- Corticosteroids impair the ability of phagocytes to clear the fungi

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- In the updated consensus definition of invasive fungal diseases, prolonged use of corticosteroids (defined as a dose of **0.3 mg/kg** corticosteroids for **3 weeks** in the **preceding 60 days**) has been listed as a risk factor

Other factors

- COVID-19 is associated with **endothelial dysfunction**. Autopsy studies have found severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes in patients with severe COVID-19.
- The vascular endotheliitis may provide an easy route for entry of the Mucorales into the bloodstream, further increasing the risk of complications.

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- The effect of inappropriate use of antibiotics on superadded infections is well known. *Staphylococcus aureus* and *Staphylococcus epidermidis*, which are common constituents of the nasal flora, have been shown to inhibit the growth of *Rhizopus arrhizus*
 - Indiscriminate antibiotic use and COVID-19 itself may have contributed to the CAM crisis.

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- **tocilizumab** could further increase the risk of infections in COVID-19 patients

Risk factors


- Most common reported risk factors:
 - ✓ diabetes,
 - ✓ hematological malignancies and
 - ✓ bone marrow & organ transplant , respectively
- No traditional risk factors for mucormycosis were identified in few of the subjects

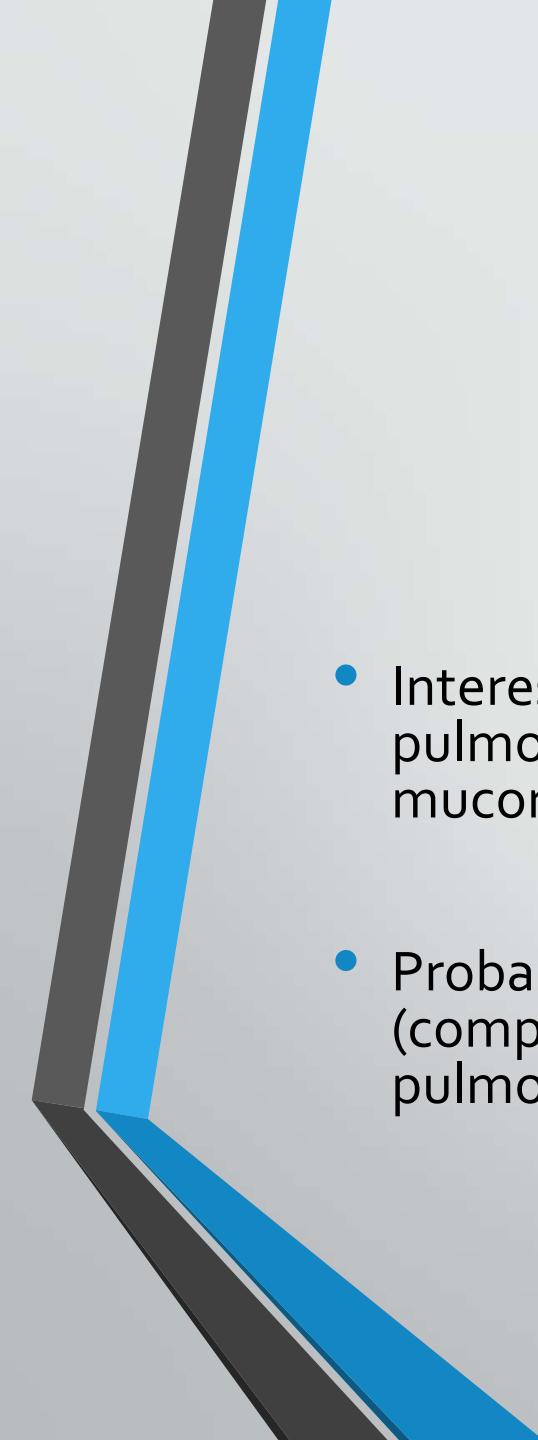
Timing of occurrence

- mucormycosis was diagnosed **simultaneously** or **within seven days** of COVID-19 were labeled as 'early CAM.'
- 'late CAM' as mucormycosis diagnosed after seven days of confirmation of COVID-19 (till a **maximum of 3 months**)
- most cases were **late** CAM (mean duration of 19.2 days)

Presentation & sites

- Overall, **rhino-orbital** (ROM) followed by **rhino-orbito-cerebral** mucormycosis (ROCM) were the most frequent presentation of CAM
- The organism responsible for CAM was primarily *R. arrhizus*, followed by *Rhizopus* spp. and *Rhizopus microsporus*.

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- Most common signs and symptoms are:
eye pain,
swollen eyes and significant lid oedema
nasal obstruction,
facial pain & hyposthesia

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- Interestingly, of the seven reported CAM cases by *R. microsporus*, six were pulmonary (including one disseminated), and the other was a case of cutaneous mucormycosis
 - Probably, the relatively smaller size of the *R. microsporus* sporangiospores (compared to *R. arrhizus*) might have lodged them in the lower airways causing pulmonary infection, which needs to be studied further.

Diagnosis

- The **suspicion** of mucormycosis is fundamental.
- **Radiologic studies**
- **Histopathological diagnosis:** biopsy of the affected tissues is the most critical form for diagnosis.
- To confirm the infection, **tissue invasion** of **unseptated hyphae** should be observed in tissue sections stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS) or Grocott-Gomori methenamine-silver (GMS), or both.

Diagnosis

- Microbiological diagnosis
- **Microscopic examination:** Microscopic examination is essential for an early diagnosis of mucormycosis. It can be performed fresh or calcofluor white (40x) and Giemsa staining (100x). Cenocytic (**not septate**), **broad (6-16 μ m)**, **branched** (usually at 90° angle) hyphae are observed.
- culture

Classification of Covid-19 associated ROCM

- **Possible:** typical signs and symptoms
- **Probable:** clinically suggestive, supportive nasal endoscopy & or supportive radiologic findings
- **Proven:** microbiological confirmation on microscopy, & or culture & or histopathology with special stains & or molecular diagnosis

management

- Treatment requires surgical debridement, antifungal treatment and, if possible, stabilization of risk factors.
- First choice, induction phase, approximately 3 weeks: amphotericin B in lipid formulations 5 mg/kg or, in case of intolerance to amphotericin B, isavuconazole, loading dose 372 mg/iv or vo/d for 6 doses, followed by 372 mg/iv or vo/d.).

treatment

- Consolidation phase: isavuconazole, loading dose, 372 mg/iv or vo c/8 h for 6 doses, followed by 372 mg/iv or vo/d, until clinical improvement or posaconazole tablets, 300 mg/d. Serum level of $> 1 \mu\text{g/ml}$ should be achieved
- (PAHO/WHO Treatment of Infectious Diseases 2020-2022 Eighth Edition, available at: <https://bit.ly/3irdeWs>)

prognosis

- pulmonary or disseminated mucormycosis cases and admission to the intensive care unit were independently associated with increased mortality

prognosis

- The reported mortality obtained in a review of literature from India (36.5%) was much lower than the previous Indian data on non-COVID-19 mucormycosis (52%) and a recently reported large study on CAM (45.7%).
- The predominance of ROM and timely treatment may partly explain the better survival reported from India.
- The paucity of pulmonary and disseminated mucormycosis cases from India suggests that these cases were either not diagnosed or reported.



Thanks for your attention