INTRODUCTION

Mucormycosis (previously known as zygomycosis), is a serious but rare fungal infection caused by a group of molds called mucormycetes. These fungi can be commonly found in soil and in decaying organic matter, such as leaves, or rotten wood. Mucormycosis largely affects population suffering from other health ailments or taking medicines that lower the body’s ability to fight germs and illness. It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also infect oral cavity or brain, gastrointestinal tract and can occur on the skin after skin injury. Important note: This is NOT “Black Fungus”.

Mucormycosis occurs when a susceptible person comes in contact with its spores in the environment. This contact can happen at the skin (spores can enter through cuts, abrasions or wounds) or respiratory mucosa (through inhalation). The fungus is ubiquitous, and the spores are commonly found in the surrounding environment. This disease is not contagious and cannot be transferred from person to person or between people and animals.

Types of mucormycosis:

- Rhino-orbito-cerebral mucormycosis (ROCM)
- Pulmonary mucormycosis
- Gastrointestinal mucormycosis
- Cutaneous mucormycosis
- Disseminated mucormycosis

Box 1: Key messages

- Mucormycosis is commonly found in the environment, soil
- Mucormycosis is not black fungus, though it looks black in colour
- Risk of mucormycosis increases in people with underlying illness like diabetes

HISTORICAL BACKGROUND

Originally, mucormycosis was described by Paltauf in 1885, as an infection from nonseptate, broad, branching hyphae typical of molds. However, the first recorded human infection with Mucorales was a case of pulmonary mucormycosis reported by Sluyter in 1847.

In 1943, the syndrome of acute orbital mucormycosis characterized by uncontrolled diabetes, unilateral internal and external ophthalmoplegia, proptosis, meningoencephalitis, and rapid death was first described by Gregory.

BURDEN

Currently India is having the second largest Covid affected population in the world with more than 2.65 crore cases as on 24th May 2021. India is also the diabetes capital of the world with nearly 7.7% of adult population being diabetic. More than 6.5 Crore people in India are diabetic (this was 2016 global burden of disease data published in lancet in 2016).
Recent times has witnessed increased cases of Mucormycosis in India. These are Covid-19 associated mucormycosis and mostly they are seen in post covid diabetic population. According to the Central government* a total of 40824 mucormycosis cases have been reported across the country out of which nearly 3229 patients have succumbed to the disease. Nearly 28186 patients are still under treatment for the same, meaning that 31% patients have been cured till date.

Very few case studies or case series have been published as of now related to Covid-19 associated mucormycosis and a review conducted in May 2021 suggested 101 cases worldwide which is only a fraction of actual cases. The article also mentions that nearly 80% are being observed in males and nearly 80% have pre-existing diabetes mellitus. The associated mortality was nearly 30%.

**Reports from various states**

Recent times has witnessed increased cases of Mucormycosis in India. While the total number of mucormycosis infections is not yet known, more than 1,000 such cases has been registered till mid-May’ 2021.

Twenty-three mucormycosis cases in AIIMS Delhi with 20 of them COVID-19 positive, and about 500 cases from other states. Reportedly, such cases are reported from Gujarat, Uttar Pradesh and Rajasthan too with associated mortality reported from Jabalpur in Madhya Pradesh and Thane in Maharashtra. Jabalpur reported three deaths of mucormycosis from May 1 to May 10 2021. About 10 people have lost vision while 40 others were undergoing treatment in Bhopal, Indore, Khandwa, Jabalpur, and Gwalior. From the eastern part of country, Odisha also reported its first case of COVID-19 related mucormycosis around 10 May 2021.

In Jaipur, Rajasthan; Sawai Man Singh (SMS) hospital reported 14 cases. While before COVID-19, hospital reported only one or two cases annually, in contrast to current trend of seen 2-3 cases daily with more of ocular involvement. Rajasthan State government has declared the disease as an “Epidemic” in the State.

At least 70 cases of mucormycosis have been detected in Hyderabad in the month of April’ 2021 with and at least six patients died of it from April 2021 to May 2021. In Apollo Hospitals only, around 50 such cases were reported. Telangana government has declared mucormycosis as notifiable disease under the Epidemic Diseases Act 1897.

Karnataka declared mucormycosis as a notified disease, after registering 97 cases wherein 4 patients lost their lives till 17 May 2021. A high mortality is observed in Maharashtra, where 52 patients died since COVID-19 outbreak in the state.

Recognizing the outbreak of Mucormycosis in the State, the government of Haryana has passed regulations under Section 2 of the Epidemic Diseases Act 1897. The state of Chhattisgarh also reported more than 70 such cases till mid-May 2021.

**AGENT**

Mucormycetes, the group of different types of fungi can cause mucormycosis. The most common causative agents are Rhizopus species and Mucor species. Other causative fungi are Lichthemia, Rhizomucor, Apophysomyces, Syncephalastrum species, Cunninghamella, etc. Belonging to the scientific order Mucorales, these mucormycetes live throughout the environment.

Humans acquire the infection predominantly by inhalation of sporangiospores, occasionally by ingestion of contaminated food or traumatic inoculation. They are more common in soil with decaying organic material, compost piles animal dung, and also present in the air.
Population at risk- All those who have lowered immunity are at an increased risk as this is an opportunistic infection. The list can include people who have the following:

- Post COVID-19 recovered population
- Elderly male population
- Uncontrolled hyperglycaemia with or without diabetes mellitus
- Malignancy (Eg: Leukaemias, Lymphomas, Aplastic anaemia, Thalassemia)
- Immunocompromised patients
- Organ transplant
- Stem cell transplant
- Iron overload (COVID-19, Bone-marrow transplantation, hemochromatosis, Therapy with iron chelators such as Desferrioxamine)
- Neutropenia, Monocytopenia
- Long-term corticosteroid use
- Intravenous drug abuse
- Skin injury due to surgery, burns, or wounds
- Prematurity and low birthweight (for neonatal gastrointestinal mucormycosis)
- Tuberculosis
- Patients living with Human immunodeficiency virus
- Chronic kidney disease
- Hepatitis-B and other Chronic Liver diseases
- Chronic alcoholics and smokers
- Cancer Chemotherapy
- Prolonged ICU stay
- Immunosuppressive therapy as part of COVID-19 treatment

CASE DEFINITION

In COVID-19 settings the most common presentation is either rhino orbital or Rhino-orbito-cerebral (ROC) Mucormycosis. The patients can be categorized as Possible (Suspected), Probable, and Proven (Confirmed).

1. A patient who has symptoms and signs of rhino-orbital or ROCM in the clinical setting of concurrent or recently (<6 weeks) treated COVID-19, diabetes mellitus, use of systemic corticosteroids, mechanical ventilation, or supplemental oxygen to be considered as Possible ROCM.
2. A patient with clinical symptoms and signs of rhino-orbital or ROCM supported by CT scan, or contrast-enhanced MRI, diagnostic nasal endoscopy findings, the patient to be considered as Probable case.
3. A probable case with microbiological confirmation of tissue sample on direct microscopy (KOH mount) or culture or histopathology with special stains is to be taken as confirmed case.

Analysis of biological specimens from clinically involved sites is mandatory for confirmation. Every effort should be made to obtain tissue biopsies, e.g. endoscopic guided nasal tissue, aspirate, deep swab, nasal mucosal biopsy for histopathology, direct microscopy and culture. Where this is not possible, nasal scrapings can be collected for direct microscopy and culture, however this is not a very reliable sample. Debrided/resected tissue after surgery may be sent for direct microscopy, culture in normal saline and for histopathology in formalin.

Early warning signs of Mucormycosis

Fig:1 Brown-black necrotic patch / ulcer on palate
Most common form of mucormycosis is Rhino-orbito-cerebral followed by cutaneous and pulmonary mucormycosis. In addition to the general signs and symptoms, some of the specific systemic signs and symptoms can be-

**Rhino-orbito-cerebral mucormycosis**
- Nasal congestion
- Nasal discharge
- Localized pain
- Facial swelling or numbness
- Headache or orbital pain
- Nasal or sinus congestion
- Toothache
- Loosening of maxillary teeth
- Jaw involvement
- Blurred or double vision with pain
- Paresthesia
- Fever

Skin lesion: thrombosis, necrosis, black lesions on nasal bridge or upper inside of mouth that quickly become more severe.

**Pulmonary mucormycosis**
- Chest pain
- Pleural effusion
- Hemoptysis
- Worsening of respiratory symptoms

**Cutaneous mucormycosis**
- Blisters or ulcers
- Black infected area with pain, redness and warmth around the wound

**Gastrointestinal mucormycosis**
- Abdominal pain
- Nausea and vomiting
- Gastrointestinal bleeding

**Disseminated mucormycosis**
- In this form, the infection spreads to other areas of the body and becomes widespread (disseminated)
- If infection is disseminated to the brain and patients can present with altered sensorium or coma
- Other areas that can be affected include the heart, kidney, spleen, skin, and other organs.
The symptoms vary according to the system being affected. If the earliest sign is oro-facial pain and swelling then the patient may contact a dentist, if it is pain or pressure in the eye then the ophthalmologist is contacted, if it is fever associated with headache and nasal congestion then it is an ENT surgeon and if there is shortness of breath of chest pain then it can be a pulmonary medicine or medicine physician. Very often these patients tend to consult their family physicians first, hence it is important to educate the medical fraternity at large.

**DIAGNOSIS**

The finding of any of these signs should prompt immediate further testing:

**Nasal Endoscopic Examination**
- Black Necrotic tissue and eschar

**Blood tests**
- CBC (Look for neutropenia / monocytopenia, Raised ESR)
- FBS, PPBS, HBA1C
- LFT, RFT with electrolytes
- HIV, HBsAg

**Radiographic imaging**
- X-Ray PNS (Para Nasal Sinuses) and OPG (Ortho-Pantomogram) – can be normal
- CECT of PNS and Orbit – Erosion and thinning of hard tissues, mucosal thickening of sinuses, enlargement of masticatory muscles
- Contrast MRI – Optic neuritis, intracranial involvement, CST, Infratemporal fossa involvement
- HRCT Chest - Reverse halo sign: nodule (≤3 cm)/ mass (>3 cm) or consolidation with surrounding ground-glass opacity halo, central necrosis and air-crescent sign

**Biopsy**
Nasal cavity for ROCM, if palatal involvement then biopsy from oral cavity, Transbronchial biopsy and BAL (for Pulmonary). CT guided FNAC can be considered in some cases of Pulmonary Mucormycosis.

**Histopathology**

Broad ribbon-like, thin-walled, primarily aseptate or pauci septate hyphae that have irregular diameters; with non-dichotomous irregular branching and accompanying tissue necrosis and fungal angioinvasion. (Grocott Methenamine Silver GMS and Periodic Acid-Schiff PAS stains).

**Box 2: Key messages (diagnosis)**
In addition to the above listed signs and symptoms, the following should be considered as red flag to initiate testing: cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital swelling, orbital apex syndrome or a palatine ulcer.

Fig: 6 GMS staining of Mucormycosis Source Lancet- MSGERC study-2019

Fig: 7 H&E staining of Mucormycosis Source Lancet- MSGERC study-2019

Fig: 8 KOH mount from sputum sample 1 from VPCI lab, Delhi
Direct microscopy - KOH mount (or fluorescent wet mount): an inexpensive, yet invaluable method to rapidly give a presumptive diagnosis. Mucorales are seen as broad ribbon-like, thin-walled, primarily aseptate or pauci septate hyphae that have irregular diameters; with non-dichotomous irregular branching.

Culture and sensitivity testing – Mucorales grow on any carbohydrate substrate. Colonies appear usually within 24–48 h and identification is based on colonial / microscopic morphology and growth temperature. Matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) can be used in equipped settings. The major concern about culture, however, is its low sensitivity, as it can be falsely negative in up to 50% of mucormycosis cases. Hence a combination of clinical and laboratory work up is essential to arrive at the actual diagnosis.

Molecular methods – Molecular techniques such as PCR can be used to identify this fungus directly from the infected tissues or from bronchialveolar lavage. However, these tests require invasive sampling (biopsy, bronchialveolar lavage). Recently, Mucorales DNA detection in non-invasive specimens like serum have been found to be effective for early diagnosis of mucormycosis.

Serology - There are no commercially available antigen markers to detect Mucorales. β-D-glucan test and Aspergillus galactomannan tests do not detect antigen components of the Mucorales cell wall. These two tests can help to rule out invasive aspergillosis, the most frequent differential diagnosis, or combined Aspergillus and Mucorales infections.

Few additional points on Mucor and COVID-19

- Increase in ferritin level is commonly seen in COVID-19 patients. Iron overload can lead to increased susceptibility to Mucormycosis.
- Prolonged use of higher end antibiotics can kill the bacterial commensals, leading to proliferation of fungal commensal such as Rhizopus or Mucor and generating a susceptible environment to cause Mucormycosis.
- Excessive use of steroids can aggravate hyperglycaemia and in turn create a conducive environment for proliferation of fungi.
- Intubation, Mechanical ventilation, Chronic respiratory disease can lead to damaged epithelial and endothelial tissues – site for fungal angioinvasion.
- Besides, the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients always have immunosuppression with a decrease in CD4+ T and CD8+ T cells. Severe form of COVID-19 illness is also found to reduce the level of lymphocytes as well as neutrophils. Both of which increase the chances of getting Mucormycosis infection.
Use of steroids and broad-spectrum antibiotics in COVID-19, coupled with uncontrolled hyperglycaemia has found to have increased the incidence of mucormycosis. Mucormycosis can be seen in both active COVID-19 patients and in post-recovered individuals. Case fatality rates of mucormycosis according to previously reported data are as high as 50-70% and hence, prime importance should be laid on preventing the occurrence of this disease and eliminating all the risk factors leading to the infection in future. Per reports, prevalence of CAM is more among patient with diabetes. Hyperglycaemia affects the immunity and also provides favourable environment for the growth of fungi.

### Primary Prevention
- Proper usage of masks (universal)
- Avoid activities that involve contact with soil or dust, such as dusting or yard work or gardening
- Hand-hygiene is a good way to avoid transferring infection from hands to the respiratory mucosa
- Proper wound care (Surgical dressing, usage of antiseptic, debridement)
- Strict glycaemic control and regular blood glucose monitoring
- Strict adherence to Anti-Diabetic medications
- Post COVID follow up and daily blood glucose monitoring in previously non-diabetics as well
- Diet and Lifestyle modifications for preventing Diabetes
- Cessation of smoking and alcohol
- Avoidance of self-medication
- Compulsory Health education to patients suffering from Covid-19 and those who have been discharged from either home isolation or facility-based treatment

### Secondary Prevention
- Mass chemoprophylaxis is currently not recommended
- Currently no vaccine is available for prevention of Mucormycosis
- PNS endoscopy in post COVID-19 patients who are at increased risk of development of mucormycosis (such as uncontrolled diabetics) for two months
- Judicious use of antibodies/ antifungals and steroids

Early detection of mucormycosis as well as risk factors/ associated comorbidities can help prevent severe form of disease, disability, invasive treatment and death.

### MITIGATION STRATEGIES
- Stress on universal case definition, methods of diagnosis and treatment
- Continued education of treating physicians, surgeons, oral and dental surgeons, pathologists, radiologists, and microbiologists regarding mucormycosis
- An Integrate Disease Surveillance Program (IDSP) based surveillance system to identify the burden of disease in the country
• Investment on Research and Development in producing highly effective and specific pharmacotherapy

**TREATMENT**

The overall management of mucormycosis should be started as early as possible. Management can involve consultation with various experts like infectious disease specialist, microbiologist, histopathologist, intensivist, pulmonologist, neurologist, ENT specialist, ophthalmologist, dentist, surgeons, and radiologists. People who are suspected of having mucormycosis should contact their nearest healthcare provider at the earliest and then seek care from the above listed specialists as per the involvement of the organ.

**Box 3: Basic principles of treatment**
- Strict control of hyperglycaemia is vital
- Steroids are lifesaving drugs in COVID-19 patients, but abuse / misuse / untimely use must be avoided
- Judicious immunomodulating drugs
- Surgical debridement: Infected tissues are generally removed through surgical procedure at the earliest
- Monitor patients clinically, with radiography for response / disease progression & microbiologically
- After 3-6 weeks of amphotericin B therapy, consolidation therapy for 3-6 months

**Treatment algorithm**
- The following recommendation for the treatment of CAMs is considering the evidence available
- The following algorithm is generic and should be used as a guiding tool but used judiciously by treating physicians as per the case at hand
- Special considerations must be made by the multidisciplinary treatment teams while considering extensive surgical debridement regarding future disability and quality of life of the patients
- This has been recommended by FISF in their recent guidelines specifically for treatment of Covid-19 associated mucormycosis (figure 12)
- ICMR Advisory for screening, diagnosis and management of covid-19 associated mucormycosis are at figure 13
- The guide box on managing covid-19 associated mucormycosis by DGHS are at figure 14
- The clinical guidelines from All India Institute of Medical Sciences (AIIMS), New Delhi are at figure 15.
Figure 12: FISF recommendations on Treatment of Covid-19 associated mucormycosis

1. Diabetes control
2. Reduce steroids
3. Discontinue immunomodulators

Liposomal/lipid amphotericin B
- 5mg/kg/day for 3-6 weeks
  - 1. In 200mL 5% dextrose over 2-3h
  - 2. No slow solution
  - 3. In CVC infection, dose can increase to 10mg/kg/day
  - 4. Monitor NT, potassium & magnesium levels

Lipid amphotericin B
- Not available

Polyene not available or intolerant to polyene

Polyene/hivaconazole/posaconazole not available

Amphotericin B deoxycholate
- 1-1.5mg/kg/day for 3-6 weeks
  - 1. In 500mL 5% dextrose over 6-8 hours
  - 2. Pre-medication to avoid infusion reaction
  - 3. No slow solution
  - 4. Monitor NT, potassium & magnesium levels

Itraconazole
- 200mg tid for 2-6 weeks
- Monitor LFT every week
- Monitor for fever
- Stop proton pump inhibitor, if needed when itraconazole used
- Consume along with food
- TDM after 3 days is recommended

Posaconazole
- 300mg on day 1 & then 200mg bid for 3-6 weeks
- Monitor trough levels after 5-7 days

Itraconazole tab – 200mg tid on day 1 & then 200mg bid for 3-6 months
OR
Posaconazole tab – 300mg on day 1 & then 300mg bid for 3-6 months
(Monitor trough levels after 3-5 days)

1. Shift to azoles, if the patient is on polyene
2. Shift to ivaconazole, if drug interaction with posaconazole

http://www.fisftrust.org

May 20, 2021
Figure 13: Advisory from ICMR regarding COVID-19 associated Mucormycosis

Figure 14: Clinical Guidebox from DGHS COVID-19 associated mucormycosis
The government has requested all the states to notify Mucormycosis through the use of a case reporting format provided on the covid portal. The IDSP district surveillance unit in coordination with the district level administration must collect the relevant data so as to capture a better picture of the disease and the factors associated with sudden apparent rise in cases. The SOPs for reporting Mucormycosis from District/State are as follows:

- **Mucormycosis** is a fungal infection that mainly affects people who are on medication for other health problems that reduces their ability to fight environmental pathogens. Currently, Country is witnessing an apparent rise in number of Mucormycosis cases among patients hospitalised for management of COVID-19. These cases have also been observed to have worse clinical outcomes & high mortality.

- In this context, there is a need to have a standard reporting system for Mucormycosis cases observed among confirmed COVID-19 as well as non-confirmed COVID-19 cases from government and Private facilities managing such cases. Due to its spread & high mortality such cases are majorly being reported from tertiary care hospitals.

- Provision of daily reporting of Mucormycosis cases has been made in covid portal. District Surveillance Officer will be overall responsible of reporting Mucormycosis cases in S3 portal being managed in tertiary level Government and Private health care facilities in his/her district.

- The daily flow of information from tertiary level Government and Private health care facilities to District Health Department (DSO) and its subsequent entering in S3 portal by the DSO will be facilitated by District Magistrate/Collector. It is extremely crucial to have a smooth flow of desired information from Medical institutions to Health Department.

- Regular sensitization meetings under the Chairmanship of DM/DC may be conducted to streamline the flow of information.
**Form for Epi Data Collection (suggestive)**

### GENERAL INFORMATION
(in case any follow up information is required)

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### PATIENT INFORMATION

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### COVID TREATMENT TAKEN

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### INVASIVE FUNGAL DISEASE (IVD)

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| Type of Presentation (Tick all that apply): Orbital/periorbital/Rhino/sinusitis (maxilla/sphenoid/frontal)/cerebral/bilateral/unilateral/palate/teeth/cavernous sinus thrombosis/fungal pneumonia/ | |
|                                                                                                                                   |

| Diabetes mellitus status: Known Diabetic: Yes/No. If yes, no. of years since diagnosis: |
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| Blood sugar at time of presentation with IFD: | highest recorded blood sugar during COVID treatment: |
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| Time of IVD diagnosis or before: Neutrophil counts: | Lymphocyte count: |
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<th>Surgery done: Yes/No. After how many days of IFD diagnosis:</th>
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<th>Procedure done:</th>
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<th>Outcome: Survived/Died (date of death):</th>
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References:


8. FISF recommendation mucormycosis.pdf.


17. https://www.freepressjournal.in/india/more-than-70-cases-of-mucormycosis-detected-in-chhattisgarh


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