Government of Manipur
Directorate of Health Services

Technical Guidelines for Screening, Diagnosis and Management of Covid-19 Associated Mucormycosis (CAM)

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1. Introduction:

Mucormycosis is a very rare infection. It is caused by exposure to mucor (a type of fungus) which is commonly found in soil, plants, manure, decaying fruits and vegetables. It affects the sinuses, causing pansinusitis. It can spread rapidly even overnightly to the eyes, brain, jaws and lungs and can be life-threatening in diabetic or severely immune- compromised individuals, such as cancer patients or people with HIV/ AIDS and nowadays in patients on steroids for treating Covid infection.

Since the onset of COVID-19 pandemic, there have been multiple reports across India of very high incidence of mucormycosis among patients with COVID- 19 especially in those who are diabetic and those who have received steroids and immunosuppressants like Tocilizumab. It is believed that mucormycosis, which has an overall mortality rate of 50%, is triggered by the use of steroids, a life-saving treatment for moderate to severe and critically ill Covid patients. Invasive mucormycosis has been observed even in patients with mild to moderate SARS-CoV-2 infections. The strongest predisposing factor appears to be hyperglycemia in undiagnosed or uncontrolled diabetic patients. Hyperglycemia leads to increased expression of endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective intracellular killing. An important virulence trait of Mucorales is the ability to acquire iron from the host which is an essential element for its growth. In conditions of ketoacidosis, free iron becomes readily available in the serum. This excess endogenous iron is efficiently taken up by the Mucorales through siderophores or iron permeases, further enhancing their virulence. These effects are greatly amplified by the use of corticosteroids and immunosuppressants in susceptible hosts. Corticosteroids themselves cause impairment in the neutrophil migration, ingestion, and phagolysosome fusion. Coupled with the potential implications of steroid-induced hyperglycemia, the COVID-19 patients with diabetes receiving corticosteroids or other immunosuppressants are exceptionally vulnerable to the development of mucormycosis.

2. Predisposing Factors:

2.1. Case of concurrent or recently (<6 weeks) treated severe COVID-19.
2.2. Uncontrolled Diabetes Mellitus, HIV/ AIDS or primary immunodeficiency diseases.
2.3. Immunosuppression by steroids (any dose used for >3 weeks or high dose >1 week).
2.4. Treatment with Immunomodulators: Tocilizumab, JAK inhibitors, etc.
2.5. Prolonged ICU stay.
2.6. Prolonged neutropenia.
2.7. Trauma, burns, IV drug abusers.
2.8. Long standing oxygen therapy: Especially by nasal prongs.
2.9. Comorbidities: post-transplant, malignancies.
2.10. Voriconazole therapy, deferoxamine or other iron overloading therapy.
2.11. Long term Ryles tube feeding.
2.12. Humidifier bottle contamination.
2.13. Prolonged use of higher antibiotic.
2.14. Contaminated adhesive bandages, adjacent building construction, wooden tongue depressors, and hospital linens.
2.15. Chronic Kidney Disease/ Chronic Liver Disease, and malnutrition in low birth weight infants

3. **Prevention:**

3.1. Environmental cleanliness to have NO exposure to decaying organic matters (breads/ fruits/ vegetables/ soil/ compost/ excreta etc.)

3.2. Control hyperglycemia.

3.3. Glucose monitoring in COVID 19 pat ients is requiring steroid therapy.

3.4. Optimally steroid usage- right timing of initiation, right dose, and right duration.

3.5. Use clean distilled water for humidifiers during oxygen therapy.

3.6. Use antibiotics/ antifungals only and when indicated.

3.7. Do not consider all the cases with blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/ or Covid-19 patients on immune-modulators.

3.8. Simple tests like papillary reaction, ocular motility, sinus tenderness and palatal examination should be a part of routine physical evaluation of a Covid-19 patient.

DOs	DON'Ts
Control of hyperglycemia - - To maintain between 130-180 mg/dl in ICU and strict control in wards. - HbA1C to be kept below 6.5	Don't miss warning signs and symptoms
Monitoring blood glucose levels post- COVID19 discharge and also in diabetics.	Don't consider all (cases of blocked nose as cases of bacterial sinusitis, especially in context of immune-suppression and/ or Covid-19 patients on immune-modulators.
Judicious use of steroids- low dose for 7 days only in hypoxic patients.	Don't hesitate to seek aggressive appropriate investigations (KOH staining and microscopy, culture) to detect fungal etiology.
Use of clean, sterile water for humidifiers during oxygen therapy.	Do not lose crucial time to initiate treatment for mucormycosis.
Judicious use of antifungals and antibiotics.	

4. **Suspect:** (In COVID-19 patients, diabetics or immunosuppressed individuals)

4.1. Sinusitis: nasal blockade or congestion, nasal discharge (blackish/bloody)- thin, non-purulent & foul smelling, local pain on cheek bone.

4.2. One sided facial pain, numbness or swelling.

4.3. Blackish discoloration over bridge of nose or palate.

4.4. Toothache, loosening of teeth, jaw involvement, swollen gums.

4.5. Blurred or double vision with pain; fever, skin lesion; ptosis; thrombosis and necrosis (eschar).

4.6. Loss of vision (early or late feature).

4.7. Chest pain, pleural effusion, hemoptysis, worsening of respiratory symptoms.

4.8. Seizures, stroke- in cases of cerebral involvement

5. **Examination Findings suggesting Mucormycosis:**

5.1. **Facial swelling.**

5.2. **Facial discoloration.**

5.3. **Ptosis.**

5.4. **Proptosis.**

5.5. **Restricted extra-ocular movements.**

5.6. Central Retinal Artery Occlusion.
5.7. Ophthalmoplegia.
5.8. Panophthalmitis.
5.9. Palatal eschar.
5.10. Nasal eschar.

6. Classification of Mucormycosis:
(based on clinical presentation)

6.1. CAM (Covid-19 Associated Mucormycosis)- commonest manifestation is Rhino-orbito cerebral mucormycosis [ROCM].
6.2. Pulmonary mucormycosis.
6.3. Gastrointestinal mucormycosis- rarely seen in neonates.
6.4. Disseminated mucormycosis- seen in the setting of diabetic ketoacidosis or severe immunosuppression.
6.5. Primary cutaneous mucormycosis

7. Investigations:
7.1. CBC (Complete Blood Count); LFT; Blood sugar levels- FBS, PPBS; HbA1C; KFT with Sr electrolytes.
7.2. Deep nasal swab for Gram, KOH and Calcofluor White stain + fungal culture.
7.3. Diagnostic nasal endoscopy; FESS.
7.4. CT PNS; MRI Orbit, PNS and Brain with contrast.
7.5. CT guided biopsy from lung for direct microscopy and culture (in sterile normal saline) and histopathology.
7.6. Bronchoscopic broncho-alveolar lavage for direct microscopy and culture (in sterile normal saline) and histopathology (formal saline).

[To rule out Covid Associated Pulmonary Aspergillosis (CAPA), consider sending serum samples or BAL for Beta D Glucan testing at Dept. of Microbiology, RIMS. Repeated negative test suggest mucormycosis].

8. Management:
Mucormycosis is a medical emergency and should be started on empirical therapy even prior to diagnostic confirmation. Clinicians, microbiologist, histopathologist, intensivist, neurologist, ENTspecialist, ophthalmologist, dentist, surgeons, radiologists, Covid care doctors etc. have roles in the management.

8.1. Control of diabetes & diabetic ketoacidosis.
8.2. Reduce steroids if patient is still on with aim to discontinue rapidly.
8.3. Discontinue other immune-modulating therapy like Tofacitinib/ baricitinib.
8.4. **Medical treatment**.

- Secure peripherally inserted central catheter (PICC line) or larger bore IV cannula.
- Maintain adequate systemic hydration
- Infuse normal saline IV before Amphotericin B infusion.

a. Inj. Liposomal Amphotericin B (L-AmB): is the preferred formulation from the efficacy point of view (enhanced CNS penetration) and less renal toxicity. Aphotericin B (crystalline) may be used if affordability and cost factor is a major concern. However, if the patient has deranged KFT/ LFT or the patient does not tolerate then Amphotericin B (Liposomal or Lipid) should be used.

5 mg/ kg/ day in 200 cc 5% dextrose, given over 2-3 hours infusion for 2 weeks [higher dose 7.5 mg to 10 mg/ kg/ day may be given in brain involvement].

OR

b. Inj. Amphotericin B Deoxycholate (D-AmB) [if cost/ availability of L-AmB is an

issue]:

i. 1 mg / kg / day in 5% dextrose, slow infusion for 6-8 hours for 2 weeks.

ii. Pre-medication: (NSAIDs and/or diphenhydramine or acetaminophen with diphenhydramine or hydrocortisone) Pre infusion administration of 500 to 1000 ml of normal saline.

[Disadvantages - Highly toxic, poor CNS penetration].

OR

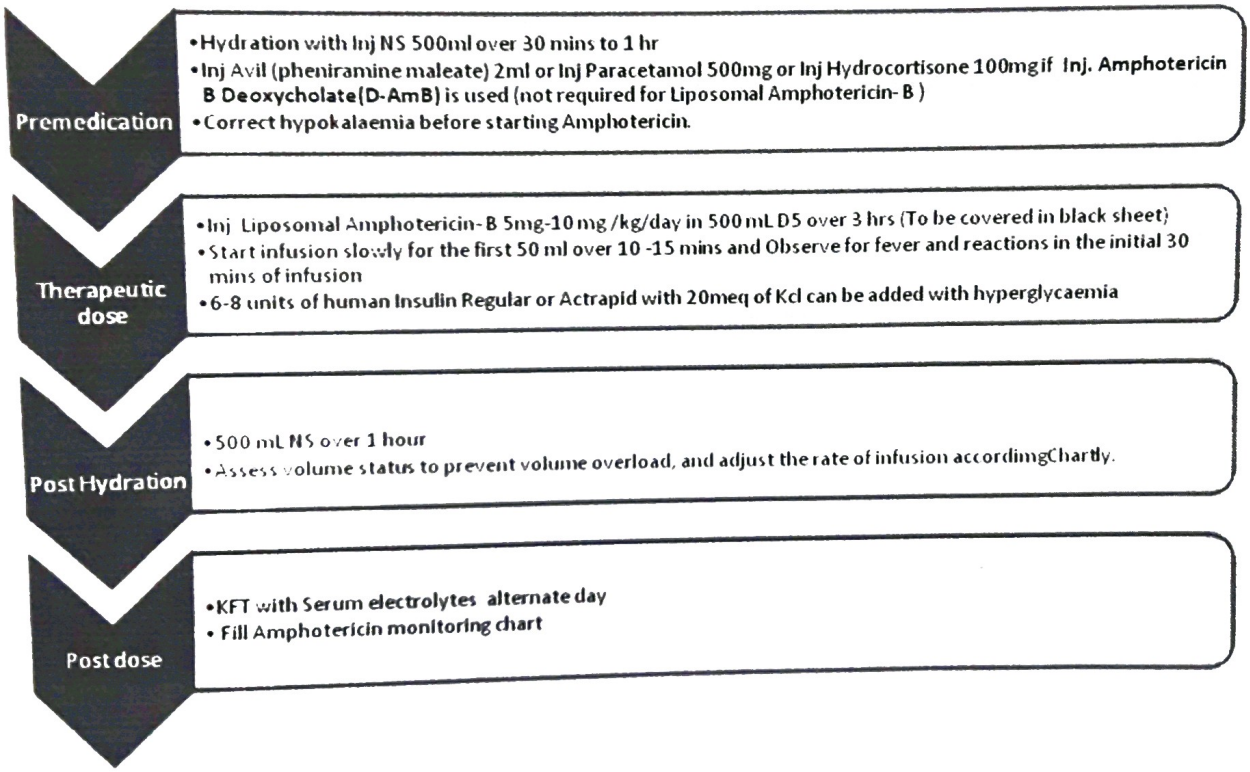
c. Inj. Amphotericin Lipid Complex (ABLC):

i. 5 mg/ kg/ day for 2 weeks.

[Advantage: less nephrotoxic than D-AmB]

[Disadvantage: expensive, possibly less effective than L-AmB for CNS infection]

Flow Chart of Amphotericin B administration:



Amphotericin Monitoring Chart(To be filled daily)															
Sl. No	Name of the drug	Date	Starting time	Ending time	Daily dose	Cumulative dose	Serum Electrolytes					Urine Output	Premeds	complication	Remarks
							BU	Cr	Na	K	Mg				

8.5. **Surgical treatment- urgent surgical debridement: Extensive to remove all necrotic materials.**

a. Early surgical debridement of sinuses [All patients].

b. Transcutaneous Retrobulbar Amphotericin B (TRAMS): 1 ml of 3.5 rng/rnl [Select cases only].

c. Orbital Exenteration: For patients with extensive orbital involvement.

In follow-up of this patient, recurrence should be closely monitored.
Strict long term diabetic control is needed for the same.
As surgical treatment involves disfigurement of face, consultation of a plastic surgeon can be sought.

9. Practical protocol to be followed:

9.1. Baseline blood sugar and HbAlc (if available) on admission.

9.2. Strict control of blood sugar levels (110-180 mg/dl) and Diabetic Ketoacidosis(DKA).

9.3. Rational use of steroids in the high risk group.

9.4. Adequate humidification with distilled water used in the humidifiers of the Conventional/ low Flow/ High Flow Oxygen delivery system.

9.5. Maintain hygiene of Oxygen delivery system.

9.6. Complete ENT Evaluation:
At the time of discharge of a completely recovered RT-PCR positive and RT-PCR negative cases, with High-Risk factors.

- Diagnostic Nasal Endoscopy (DNE) + Otoscopy + Palatal Examination.
- Deep Nasal Swab for KOH smear & Fungal Culture.
- If possible take a biopsy specimen (in sterile saline for mycology & formal saline for histopathology) spot or any time.
- Start Amphoterecin-B (in very high clinical and radiological suspicion) without waiting for Microbiology Reports.

9.7. Complete Ophthalmological Evaluation: At the time of Discharge of a completely recovered COVID +ve with High-Risk factors.

To examine the patient for early clinical signs of mucormycosis in Anterior & Posterior Segment of eye (Congestion/ Chemosis/ Pupillary Reaction/ Motility/ Central Retinal Artery Occlusion)

9.8. **Criteria for examination by an ENT specialist & if required by Ophthalmologist on discharge. If the patient has had any of the following during admission:**

a. **Blood sugar level>200.**
b. **HbIAC** > 8.
c. **Oxygen therapy > 7 days.**
d. **Steroid therapy > 7 days.**
e. **Use of Tocilizumab/ Baricitinib.**
f. **ICU stay > 7days**

9.9. Radiological Evaluation:
Plain MRI PNS & Orbit to be done at any point, in very high clinical suspicion.

a. During the course of Admission.
b. At the time of discharge of recovered Covid patients (irrespective of RT-PCR test status) with very high clinical suspicion.

9.10. **Advice to Patient & Care Giver (At Discharge):**
Inform the patients about the early signs and symptoms of mucormycosis.

a. Nasal Blockage.
b. Blood tinged/ blackish nasal discharge.
c. Headache.
d. Pain in the eye.
e. One sided facial pain & swelling or numbness.
f. Toothache, loosening teeth, discomfort during chewing.

g. Swelling of Eye & Adnexa.
h. Double Vision

NOTE:

- Immediately consult your treating Otorhinolaryngologist/ Ophthalmologist, if you experience any of the afore-mentioned signs and symptoms.
- Follow up on Day 7 and at 3 weeks.

[Definition of High-Risk Group: All COVID-19 cases with uncontrolled DM + DKA / T2DM on Insulin with high dose Corticosteroids + Immuno-modulators and require oxygen delivery systems].

10. SOP for strict adherence of humidifiers

10.1. Always use distilled water or sterile water.

10.2. Never use un-boiled tap water nor mineral water.

10.3. Fill up to about 10 mm below the maximum fill line and do not let the water level pass below the minimum fill line.

10.4. Water level should be checked twice daily and topped up when required.

10.5. Water in the humidifier should be changed daily.

10.6. Humidifier should be washed in mild soapy water, rinsed with clean water and dried in air before reuse.

10.7. Once a week (for the same patient) and in between patients, all the components of the humidifier should be soaked in mild antiseptic solution for 30 minutes, rinsed with clean water and dried in air

NOTE: All patients at risk of developing mucormycosis [those with uncontrolled diabetes mellitus, chemotherapy, post-transplant, long term steroids and Covid 19 moderate to severe disease] should ideally avoid construction sites as air near construction sites will be full of fungal spores and the Immuno-compromised are at risk of developing COVID associated pulmonary aspergillosis [CAPA] and CAM.

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