

COVID ASSOCIATED MUCORMYCOSIS

MUCORMYCOSIS is a rare, non-contagious fungal infection which occurs in patients with the underlying conditions and predisposing factors such as diabetes mellitus, rampant misuse/overuse of steroids, malignancies, organ transplantation etc. Mode of infection is through inhalation of fungal spores from air. It is not contagious.

COVID19 Associated Mucormycosis (CAM) can occur with active COVID-19 infection (**concomitant**) and can occur sequentially in weeks or months following recovery (**sequential**).

COVID19 Associated Mucormycosis (CAM) based on clinical presentation is classified as:

1. Rhino-orbito-cerebral Mucormycosis (ROCM): - most common in people with uncontrolled diabetes, Post-kidney transplant
2. Pulmonary Mucormycosis: - most common in people with cancer, organ transplant or a stem cell transplant
3. Gastrointestinal Mucormycosis: - more common among young children than adults, especially premature and low birth weight infants less than 1 month of age
4. Disseminated Mucormycosis: - Occurs when the infection spreads through the bloodstream to affect another part of the body. Seen in diabetes ketoacidosis or in severe immunosuppression. Most commonly affects the brain, but also can affect other organs such as the spleen, heart, and skin.
5. Primary cutaneous Mucormycosis: - occurs after the fungi enter the body through a break in the skin (for example, after surgery, a burn, or other type of skin trauma). This is the most common form of Mucormycosis among people who do not have weakened immune systems.

Prevention

- Do not Self-Medicare even in mild cases. Always follow the instruction of a healthcare worker.
- Do not delay the reporting of symptoms/signs of Mucormycosis to the doctor.
- Do not ignore any medical advice issued by a competent authority.
- Always provide adequate history of comorbidities to your doctor, especially diabetes or any immunocompromised states.
- Maintain basic hygiene and cleanliness.
- Avoid unnecessary use of Iron supplements and Chelating agents like Deferoxamine.
- Use of Steroids must be strictly according to the State Guidelines for management of COVID19 only. The Duration of treatment with steroids should not exceed 7-10 days unless clinically indicated.
- The Oxygen Humidifiers must be cleaned every day and filled with Sterile water/Distilled Water and appropriate infection control measures must be followed.
 - Do not use Tap Water or Mineral water or Normal Saline/ Dextrose in the humidifier.
 - Fill only up to the maximum marked level.
- Once a week (for the same patient) and in between patients, all components of the humidifier should be soaked in mild antiseptic solution for about 30 minutes, rinsed with clean water and dried. A Good Glycemic Control should be maintained during the management of COVID19.
- Universal Masking should be strictly followed.
- Disposable and N95 masks to be used for 8 hours in a day and disposed. Cloth masks to be used for one day, washed, dried under the sun, and then reused.
- During discharge of the patients, advice about the early symptoms or signs of Mucormycosis
- No construction/ renovation activities with-in premises of COVID hospital
- Restricted entry inside COVID wards (Just like ICU)
- Wet Mopping of floor, patient surroundings /articles with appropriate disinfectant for every shift.

Every Case of Mucormycosis must be notified to the competent health authorities.

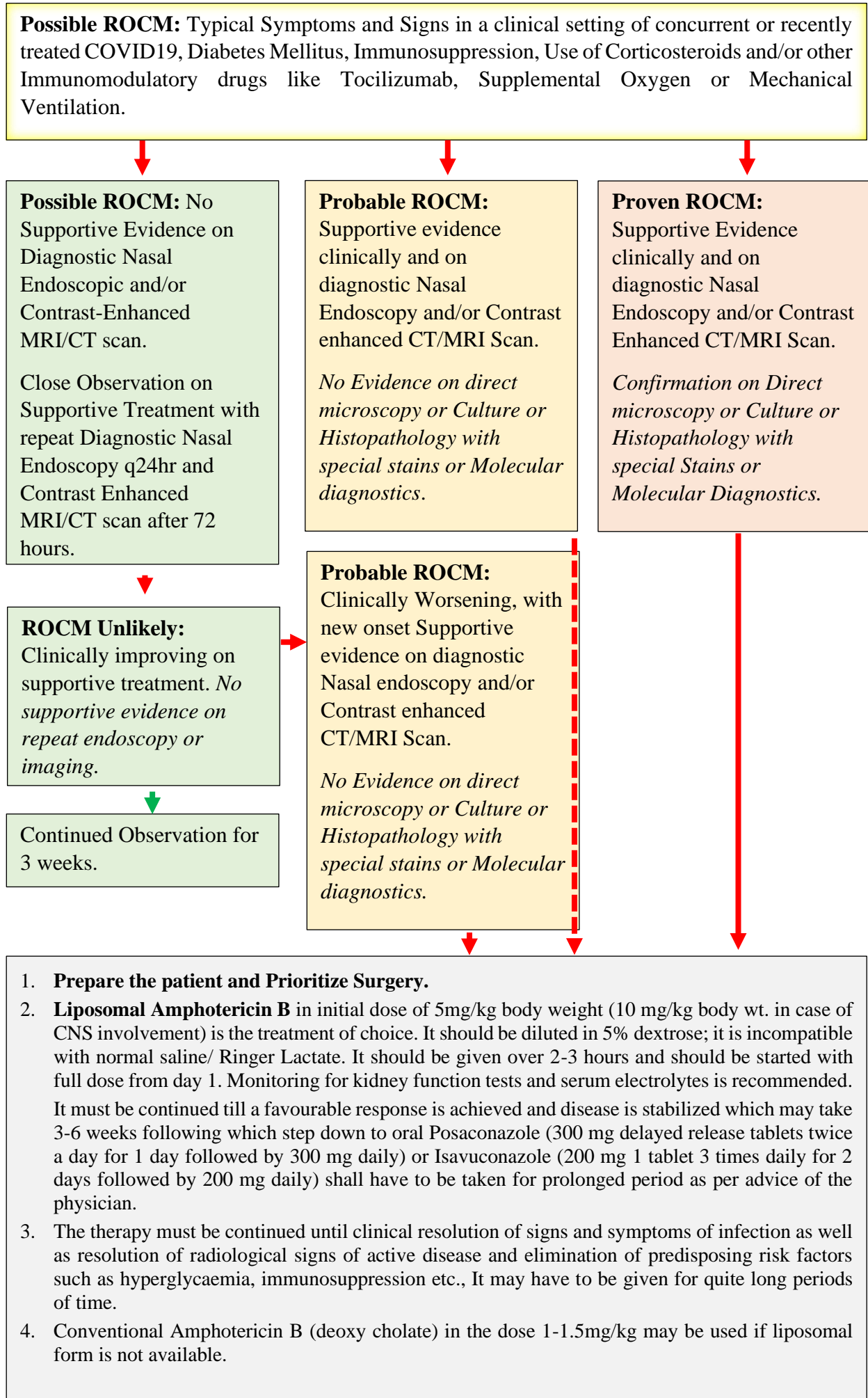
The detailed history of the case must be elucidated to know the source of fungus, and the same must be conveyed to the health authorities.

At the hospital level, each case of Mucormycosis must be audited to identify the source of infection, and the infection site must be tagged, and the Government Health Authorities must be notified about the Source of the infection that was tagged.

- Mucorales are not Black Fungi. *Black fungi are different category of fungi having melanin in their cell wall.*
- Mucormycosis is *not contagious*. It does not spread from one person to another.

<p><u>Do's</u></p> <ul style="list-style-type: none"> • Give history of diabetes to doctor • Get Sugar levels checked • Watch for early signs of Mucor listed above. • Maintain basic hygiene and cleanliness. • Follow medical advice; Take complete course of treatment as suggested by doctor 	<p><u>Don'ts</u></p> <ul style="list-style-type: none"> • Self-medicate, especially steroids • Delay reporting symptoms of Mucor • Ignore medical advice
<p><u>Sentinel Signs and Symptoms:</u> (Checklist)</p> <ul style="list-style-type: none"> • Nasal blockade or congestion, • Nasal discharge (blackish/bloody/purulent), • Local pain on the cheek bone, • One sided facial pain, numbness or swelling, • Blackish discoloration over bridge of nose/palate/around the eye, • Loss of sensation of the area, • Toothache, loosening of teeth, jaw involvement, • Intraoral pus discharge, • Ulceration & Blackening of mucosa, • Exposed palatal bone, • Sinus tract, • Blurred or double vision with pain, • Sudden loss of vision, • Chemosis, • Exophthalmos, • Ophthalmoplegia, • Fever, headache, skin lesion: thrombosis & necrosis (eschar), • Chest pain, pleural effusion, haemoptysis, worsening of respiratory symptoms, • Altered mental state, Rapid deterioration of general condition. 	<p><u>Predisposing factors are:</u></p> <ul style="list-style-type: none"> • Uncontrolled Diabetes Mellitus. • Immunosuppression by steroids/immunomodulator drugs. • Prolonged ICU stays. • Co-morbidities– Post-Transplant/malignancy/Sickle Cell Anemia. • Voriconazole therapy <p><u>When to suspect:</u></p> <ul style="list-style-type: none"> • Sinusitis – nasal blockade or congestion, nasal discharge (blackish/bloody), local pain on the cheek bone • One sided facial pain, numbness or swelling • Blackish discoloration over bridge of nose/palate • Toothache, loosening of teeth, jaw involvement • Blurred or double vision with pain; fever, skin lesion; thrombosis & necrosis (eschar) • Chest pain, pleural effusion, hemoptysis, worsening of respiratory symptom
<p><u>Pulmonary Mucormycosis:</u> Fever, Cough, Hemoptysis, Chest pain, Pleural Effusion, Worsening Respiratory Symptoms.</p> <p><u>CT Thorax:</u> Suspect Mucormycosis in patients with thick-walled Lung Cavity (Need to differentiate from COVID Associated Pulmonary Aspergillosis-CAPA), Reverse Halo Sign, Multiple nodules, Pleural Effusion. Presence of Reverse Halo Sign (Atoll Sign), more than 10 pulmonary nodules, and pleural effusion is more in favor of CAM than CAPA. <i>Presence of bronchial thickening, tracheobronchial involvement, peri bronchial collection, and tree-in-bud nodules are in favor of CAPA. Tuberculosis must be ruled out with appropriate tests.</i></p>	
<p><u>Diagnosis:</u></p> <p><u>Mucormycosis is a Medical Emergency and proper/correct context should be started on Empirical therapy even prior to diagnostic confirmation.</u></p> <ul style="list-style-type: none"> ➤ Suspected patients must undergo appropriate radio-imaging study at the earliest. MRI-PNS with brain contrast study for ROCM, and plain CT thorax for pulmonary Mucormycosis must be done. ➤ Diagnosis is confirmed by fungal staining/ culture from appropriately collected specimens. KOH mount and microscopy, histopathology of debrided tissue (presence of Ribbon like aseptate hyphae 5-15µ thick that branch at right angles). ➤ Molecular Diagnostic Methods such as Immunohistochemistry, PCR can be done. 	
<p><u>What to do if you have these symptoms?</u></p> <ul style="list-style-type: none"> • Consult your doctor immediately • Doctor will examine you clinically. If required, the doctor will take swabs from nose and test them for fungus • If the infection is strongly suspected or confirmed, you may need treatment with antifungal medications and surgery 	

Management Approach for Rhino-Orbito-Cerebral Mucormycosis.



Treatment:

Mucormycosis is a Medical Emergency and proper/correct context should be started on Empirical therapy even prior to diagnostic confirmation.

One should have a high index of suspicion of invasive fungal infection such as Mucormycosis in the presence of predisposing conditions as mentioned above. Timely initiation of treatment reduces mortality. Multidisciplinary Team approach is required. Treatment of Mucormycosis involves combination of surgical debridement and antifungal therapy.

- Liposomal Amphotericin B in initial dose of 5mg/kg body weight (10 mg/kg body wt. in case of CNS involvement) is the treatment of choice. It should be diluted in 5% dextrose; it is incompatible with normal saline/ Ringer Lactate, given through Peripherally Inserted Central Catheter (PICC) line/Central Venous Catheter (CVC). It should be given over 2-3 hours and should be started with full dose from **day 1**. Monitoring for kidney function tests and serum electrolytes is recommended. It must be continued till a favorable response is achieved and disease is stabilized which may take 3-6 weeks following which step down to oral Posaconazole (300 mg delayed release tablets twice a day for 1 day followed by 300 mg daily) or Isavuconazole (200 mg 1 tablet 3 times daily for 2 days followed by 200 mg daily) shall have to be taken for prolonged period as per advice of the physician.
- The therapy must be continued until clinical resolution of signs and symptoms of infection as well as resolution of radiological signs of active disease and elimination of predisposing risk factors such as hyperglycemia, immunosuppression etc., It may have to be given for quite long periods of time.
- Conventional Amphotericin B (deoxycholate) in the dose 1-1.5mg/kg may be used if liposomal form is not available.
- Kidney Functions must be monitored during the entire management period.

Microbiological Surveillance for COVID Associated Mucormycosis in Healthcare settings

Sample locations:

ICU/HDU/ Wards

Preference to be given to areas from where Mucormycosis cases are reported.

Method of sampling:

1. The Sabouraud Dextrose Agar (SDA) plates should be examined for contamination, prior to use.
2. Assemble the plates and ensure that the correct information is written on the base of the plate (the part containing the media) with ink or another marker. *Do not mark on the lid of the plate, as there is always a possibility of lids coming off and being replaced on the incorrect sample plate.*
The following details must be marked on each plate or recorded separately:
 - date and time of day sample taken.
 - area/location of sample.
 - position/sample number.
3. Plates must be kept in the ICU/ HDU/ Ward where they are to be exposed. Four side tables next to beds to be identified to ensure it falls within 10 cubic ft
4. Place the plates in the appropriate positions with the lids still on.
5. Raise the lids to expose the surface of the medium, rest the lid on the very edge of the plate so that the entire agar surface is completely exposed. *Take care not to put fingers on plates. Avoid passing anything over the top of plates being exposed, where possible.*
6. Leave plates exposed for one hour. The exposure time should be recorded before sending the plates for incubation.
7. After exposure:
 - Replace lids of plates.
 - clean the areas where plates have been exposed with a suitable disinfectant (70% isopropyl alcohol solution)
 - Remove from area/room/cabinet

- Collect all plates exposed, and transport in sample transportation container to department of Microbiology.
8. The following items to be swabbed and sterile swabs must be labelled appropriately:
 - a. Patient linen (dress, bedspread, and blanket)
 - b. Patient cot railings and IV Stand
 - c. Inner surfaces of Nasal cannulas or oxygen mask
 - d. Inner surface of Oxygen humidifiers
 9. 50-100 mL of water used for oxygen humidifiers should be sent in a sterile container after proper labelling.
 10. SDA plate must be exposed to oxygen outflow 21/ min for 5 minutes
 11. Complete and enclose the necessary documentation (Date/time/location)

At Microbiology Department:

Incubation conditions at Mycology section, Department of Microbiology:

Settle Plate:

1. Check the plates for appropriate label.
2. Place the plates with lids upright at 25° C incubator
3. Check next day and second day for initial growth, also rule out plate contamination
4. Take final reading on day 5 for fungal growth, speciate and record CFU/cu.ft

Swabs:

Each swab should be inoculated on separate SDA plate (appropriately labelled), incubated at 25° C and further processed similar to settle plate and any fungal growth should be speciated and recorded.

Water:

50-100 ml should be passed through membrane filter (0.4/0.2 micrometre) using 10 ml syringe, membrane should be removed aseptically using sterile forceps and area of membrane facing upwards should be inverted and placed on SDA agar plate and further reading must be taken as in settle plate method and any fungal growth should be speciated and recorded.

Oxygen:

Exposed SDA plates to be incubated and further reading taken as in settle plate method and any fungal growth should be speciated and recorded.

Laboratory Diagnosis of Mucormycosis:

Clinical Specimens: (In order of Preference)

1. Biopsy from Functional endoscopic sinus surgery (FESS)
2. Biopsy from suspected lesions.
3. Exudates from nares, hard palatal lesions, sinus material or from any suspected lesion

Following Investigations must be done on the samples:

1. Microbiology laboratory: KOH (10 %) and Fungal Culture (sample in sterile saline)
2. Pathology laboratory: HPE (sample in formalin).

KOH mount: KOH helps in screening and has short Turn Around Time.

Sample is put in 10% KOH and observed after 30 min to 1 hour to look for broad, aseptate hyphae with obtuse angle branching.

Culture: SDA with antibiotics is used for culture. Check the plates for appropriate label. Place the plate with lid upright in 25°C incubator.

Reading is taken every day up to 5 days to look for growth suggestive of any fungal growth, and, in particular, Mucorales.