



Indian Medical Association HQ

MUCORMYCOSIS

Guidelines for the Diagnosis & Management

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Dear IMAites,

Greetings,

I am grateful to our beloved National President Dr. J. A. Jayalal Sir, Hon. Secretary General Dr. Jayesh Lele Sir for giving me this opportunity to share some useful information about the dreaded fungal infection, Mucormycosis.

I am indebted to Dr. Ravi Wankhedkar Sir, Past National IMA President; Dr. Ashok Adhao Sir, Past National IMA President; Dr. Milind Naik Sir, Past National IMA Vice President; Dr. Ramkrishna Londhe, President, IMA MS; & Dr. Pankaj Bandarkar, Hon. Secretary, IMA MS for encouraging and motivating me to come up with these guidelines.

I sincerely thank Dr. Sanjay Deotale, President, IMA, Nagpur; Dr. Sachin Gathe, Hon. Secretary, IMA, Nagpur; Dr. Vijayalaxmi Shinde, MBBS, MD Microbiology, Eva Women's Clinic and Lab, Dombivali; Dr. Avinash Wase, MBBS, MD Pathology, Imm. Past President Vidarbha Association of Pathologist & Microbiologist, Nagpur; Dr. Ashish Disawal, Vice Chairman, HBI IMA MS; Dr. Samir Thakare, Secretary, Vidarbha AOI for their contribution and help.

Hope these guidelines will help all of us to diagnose and manage this potentially lethal fungal disease effectively at an early stage.

Be Safe. Take Care!

Regards!

Jai IMA!

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MUCORMYCOSIS

Fungi are the interface organisms between Life and Death - Paul Stamets

Fungal infections are most commonly associated with immunocompromised individuals. Fungal infections can be localized, systemic and invasive. Fungal infection can also have a nosocomial etiology.

Since the onset of the COVID-19 pandemic there have been multiple reports across country of very high incidence of mucormycosis (also called as zygomycosis) amongst patients with COVID-19 especially in those who are diabetic and those who have received steroids. COVID-19 Associated Mucormycosis (CAM) has been associated with high morbidity and mortality, exorbitant treatment costs and has led to shortage of antifungal drugs.

Mucormycosis is a dreaded fungal infection that mainly affects people on medication for other health problems that reduces their ability to fight environmental pathogens. It may turn fatal if uncared for. It is not a black fungus, the necrosis which it causes gives rise to black discolouration to the area involved.

AETIOLOGY

Caused by Fungus Rhizopus and Mucor of the order Mucorales mainly.

AGE / SEX

No predilection

ACQUIRED BY

Inhalation of ubiquitous spores (air borne)

AFFECTS

Mostly Paranasal Air Sinuses, Lungs, Cutaneous, Gastrointestinal, Disseminated get affected after inhalation of fungal spores from the air. It is non contagious in nature.

PREDISPOSING FACTORS

- Uncontrolled Diabetes Mellitus
- Immunosuppression by Steroids
- Prolonged ICU Stay (reused face masks for oxygen delivery, reused tubing's, unhygienically prepared swab sticks = direct inoculation)
- Co-morbidities - Post transplant / Malignancy

SIGNS AND SYMPTOMS

Rhino-orbital Involvement

- Initially nasal blockage or congestion, foul smell
- Nasal discharge - Non purulent but rather thin and occasionally blood - streaked. With time the infection progresses relentlessly to the contiguous tissues including the Orbit. Erythematous to violaceous to black necrotic eschar in nasal cavity.
- The turbinates or hard palate develops black, friable areas. Exposed palatal bone, sinus tract, halitosis.
- Facial Pain, Numbness and Redness around eyes and / or nose, sinus tract on face.
- Fever



Nasal Endoscopy



Hard Palate

- Headache, Orbital pain.
- Blurred or double vision with pain, paresthesia.



Orbital



Orbital

Teeth Involvement

- Toothache, Loosening of maxillary teeth, Jaw involvement, Swollen, infected gums.



Orbital (Eschar)



Teeth

Skin Involvement

- Thrombosis and Necrosis (Eschar), Discoloration of skin.

Pulmonary Involvement - A pulmonary and disseminated form may occur.

- Cough
- Shortness of Breath
- Chest pain
- Pleural effusion
- Haemoptysis

Cerebral Involvement - Without treatment the Frontal and Temporal lobes of the Brain, the Cavernous sinus and the other adjacent structures are involved

- Altered Mental status
- Focal seizures
- Cranial nerve involvement

WHEN TO SUSPECT - (In COVID-19 patients, diabetics, immuno suppressed individuals)

- Nasal Blockage or congestion, Nasal Discharge (blackish / bloody)
- One sided facial pain, Numbness or swelling, Headache
- Blackish discoloration over bridge of nose / palate
- Toothache, loosening of maxillary teeth, jaw involvement, swollen, infected gums
- Blurred or double vision with pain, fever, skin lesion (thrombosis and necrosis - eschar formation)
- Chest pain, pleural effusion, haemoptysis, worsening of respiratory symptoms

MANAGEMENT

Mucormycosis is a medical emergency even when clinically suspected

INVESTIGATIONS

- **LAB PARAMETERS** - CBC, ESR, FBS PPBS, HbA1C, LFT, RFT with electrolytes, HIV, HbsAg, CSF (If indicated)
- **NASAL ENDOSCOPIC EXAMINATION** - Black, necrotic eschar tissue.
- **MICROBIOLOGY** - It is important to diagnose fungal infection early. Common pathogenic fungi in respiratory system, paranasal sinuses, ocular infections are caused by filamentous mould like fungi Mucor (zygomycetes), aspergillus etc. Some dermatititious fungi are also known to cause ocular, paranasal sinus infection. Fungi causing sepsis or localized infection are common pathogenic Candida species. There is a different group of fungi causing skin, nail, hair infections like the dermatophytes, cutaneous fungi etc.

▶ **Lab Diagnosis** Sample - Sputum, tissue, blood, pus, fluid, appropriate lesion etc. Appropriate collection - Avoid mixing any unsterile saline or fluids in sample. Avoid contamination of sample. Strictly no formalin for fungal culture. Avoid swab stick if possible (less material, cotton absorbs material and its fibres interfere). Send samples in sterile container only. Tissue specimens more desirable.

Direct Microscopy by KOH mount and Gram stain commonly done. (Specialized fluorescent stains available at few labs only)

Fungal Culture - Is preferred choice standard for diagnosis for common yeast like and filamentous mould like fungi. Reporting time for fungal culture varies from 3 days to 3 weeks. Some serological tests do exist which are commonly done in tertiary laboratories only.

Molecular Identification - PCR (fresh sample needed)

▶ **Sample Collection :**

Rhino-orbito-cerebral - Consult ENT surgeon for endoscopic collection of debrided tissue / biopsy one portion in sterile water for microscopy and culture, other portion in formol saline for histopathology.

Pulmonary - Broncho alveolar lavage (BAL), mini BAL, non bronchoscopic lavage, transbronchial biopsy, CT guided biopsy from lung - process for microscopy and culture.

Fungal multiplex PCR are also done in tertiary laboratories and hospitals. It is important to correlate clinically and send appropriate adequate sample for fungal cultures. Molecular diagnostics have about 75% sensitivity and can be used for confirmation of diagnosis where available.

Diagnosed with difficulty, the fungi are characterized by ribbon like hyphae that are 6 to 50 wide, rarely separate and have a tendency to branch at right angles.

- **PATHOLOGY - Histopathology** also plays an important role in diagnosis. The tissue sample can range from nasal / sinus mucosa, turbinectomy, partial maxillectomy, alveolectomy, partial and total palatal resection, total maxillectomy with orbital exenteration. After proper grossing, tissue is subjected for formalin processing. Bone is decalcified. The histological findings include ulceration of mucosa, infarctoid necrosis. The Necrosis is prominent and it is accounted for by the propensity of hyphae to proliferate within smaller blood vessels producing thromboses. Non septate fungal hyphae infiltrating tissue, vessel, nerve or as balls over surface. Extensive inflammation and foreign body giant cell reaction, infarctoid necrosis of bone. 10% formalin is used as preservative for biopsies. Rapid diagnostic techniques such as **frozen section, squash and imprint** are very much useful if available.
- **RADIOLOGY** - Suspected patients should undergo appropriate radio imaging study.
 - ▶ **Tomograms** : are useful in delineating the extent of disease. Contrast enhanced CT scan with 3D reconstruction findings: Erosion and thinning of Hard Palate, Mucosal thickening of Sinuses with irregular patchy enhancement is an early sign, Enlargement of masticator muscle, changes in fat planes.
 - ▶ **MRI-PNS** : Ischaemia and nonenhancement of turbinates manifests as an early sentinel sign on MRI - **Black turbinate Sign**. The **fluid level** in the sinus and partial or complete sinus opacification signifies advanced involvement of paranasal sinus. Thickening of the medial rectus is an early sign of orbital invasion. Patchy enhancement of orbital fat, lesion in the area of superior and inferior orbital fissure and the orbital apex and bone destruction at the paranasal

sinus and orbit indicate advanced disease. Stretching of the optic nerve and tenting of posterior pole of the eyeball indicate severe inflammatory oedema secondary to tissue necrosis.

MRI-PNS with Brain contrast study - MRI and MR angiography help to determine the extent of Cavernous sinus involvement, Ischaemic changes to the CNS, Optic neuritis, Infra temporal fossa involvement.

- ▶ **Pulmonary - Lung CT** : Confused with COVID related shadows, suspect mucormycosis in patients with thick walled lung cavity (need to differentiate from COVID associated pulmonary aspergillosis), reverse halo sign, multiple nodules, pleural effusion.

Do's

- Control hyperglycemia (Sugar Control).
- Monitor Blood Glucose level post COVID 19 discharge and also in diabetics.
- **USE STEROIDS JUDICIOUSLY** - correct timing, correct dose and duration.
- Use Clean, sterile water for humidifiers during Oxygen therapy.
- Use Antibiotics / antifungals judiciously.

Don'ts

- Do not miss warning signs and symptoms.
- 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 immunomodulators.
- Do not hesitate to seek aggressive investigations, as appropriate (KOH staining and microscopy, culture) for detecting fungal etiology.
- Do not lose crucial time to initiate treatment for mucormycosis.

TREATMENT

Team approach is required with Infectious Disease Specialist, Microbiologist, Histopathologist, Intensivist, Neurologist, ENT Specialist, Ophthalmologist, Dentist, Surgeons (Maxillofacial, Plastic), Radiologist, Biochemists etc.

- Control Diabetes and Diabetic Keto acidosis
- Reduce steroids (If patient is still on) with aim to discontinue rapidly
- Discontinue immunomodulating drugs.

MEDICAL TREATMENT

- Insert peripherally inserted central catheter (PICC line)
- Maintain adequate systemic hydration
- Infuse normal saline IV before Amphotericin B infusion
- Antifungal therapy for at least 4-6 weeks

First Line

1. Liposomal amphotericin B (L-AmB) (Preferred treatment)

5 mg / kg / day, dilute in 200 cc 5% dextrose over 2-3 hours infusion (avoid slow escalation) higher dose 7.5 mg to 10 mg / kg / day may be given in Brain involvement.

Advantage : Less nephrotoxic , Better CNS penetration

Disadvantage : Expensive

2. Inj. Amphotericin B Deoxycholate (D-AmB) (if cost and availability of L-AmB is an issue)

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

Pre-medication : (NSAID and/or diphenhydramine or acetaminophen with diphenhydramine or hydrocortisone, Pre infusion administration of 500 to 1000 ml of normal saline may be required to avoid infusion reaction.

Disadvantages - Highly toxic, poor CNS penetration

3. Inj. Amphotericin B Lipid Complex (ABLCL) -

5 mg / kg / day

Advantage : less nephrotoxic than D-AmB

Disadvantage : Expensive, Possibly less effective than LAmB for CNS infection.

4. Monitor Renal function and Potassium level while treating with Amphotericin B

5. Patients who are intolerant to Amphotericin B , alternative agents are posaconazole or isavuconazole (Injection/Tablet)

Second Line -Azole derivatives

6. Tab Posaconazole delayed release tablets 300mg twice a day on first day, followed by 300 mg once a day taken with food. Check posaconazole trough level after 7 days of therapy and avoid interacting drugs.

7. Tab Isavuconazole; 200 mg three times a day for two days followed by 200 mg once a day.

Monitor patients clinically, with radio-imaging, for response / disease progression and microbiologically.

After 3-6 weeks of amphotericin B therapy, consolidated therapy (Posaconazole / isavuconazole) for 3-6 months.

SURGICAL DEBRIDEMENT

Extensive surgery is needed to remove all necrotic material.

Endoscopic Sinus surgery, Turbinectomy, Maxillectomy (Partial or Total), Zygoma Debridement, Debridement of Orbital Floor / Walls plus localised debridement of necrosed tissue in early localized orbital disease, Exenteration of eye, Anterior table debridement, Posterior table cranialisation, Debridement of osteomyelitic skull bone.

It is a teamwork involving ENT Surgeon, Maxillo-facial Surgeon, Plastic surgeon, Ophthalmologist, Neurosurgeon, Anaesthesiologist, Intensivist.

Patients would need to come to terms with loss of function due to a missing jaw, difficulty in chewing, swallowing, facial aesthetics and loss of self esteem. Be it the eye or the upper jaw, these can be replaced with appropriate artificial substitutes or prostheses. It is important to reassure patient about the availability of such interventions instead of leaving him to panic with sudden unforeseen loss augmenting a post-COVID stress disorder which is already a reality. Prosthetic reconstruction can be effected after surgery but interim solutions should be planned even before surgery for better outcome.

PREVENTIVE MEASURES

- Use Masks - (if you are visiting dusty construction sites) in potential infective environment.
- Frequent cleaning of premises.
- Prefer disposables in patient care areas.
- Isolation advised for hospitalized patients.
- Monitoring of Infection Prevention & Control practices in High Risk Units.
- Wise, restricted, supervised use of Antibiotics, antifungal and immunomodulator drugs, immunosuppressive drugs. Systemic steroids are to be used in patients with hypoxia and oral steroids should be avoided in patients with normal oxygen saturation on room air. If systemic steroids are used, blood sugar should be monitored. The dose and duration of steroid therapy should be limited to Dexamethasone (0.1 mg/kg/day) for 5-10 days.
- Aggressive monitoring and control of diabetes mellitus, good glycemic control (110-180mg/dl) during management of COVID-19 patients is required.
- Strict aseptic precautions while administering oxygen (sterile water for humidifier)
- Complete ENT Evaluation periodically (Day 1 & between day 3 to7)
- Complete Ophthalmological Evaluation periodically (Day 1 & between day 3 to7)
- Radiological Evaluation in very high clinical suspicious patients.
- Wear shoes, long trousers, long sleeve shirts and gloves while handling soil (gardening), moss or manure.
- Maintain Personal Hygiene including thorough Scrub Bath. Hand hygiene.
- While discharging patients from hospital, counselling about early signs and symptoms of mucormycosis (one sided Facial Pain and swelling or numbness, nasal blockage, nasal discharge, headache, pain in the eye, toothache, loosening of teeth, discomfort during chewing, swelling of eye, double or blurred vision, chest pain, respiratory insufficiency) should be done.

REMEMBER

Mucormycosis is not contagious. It does not spread from one person to other. The fungi remain in the outdoor and indoor environment. The spores enter the respiratory tract via air.

No antifungal prophylaxis is recommended as the incidence is not more than 10% in any COVID-19 cohort.

With advent of newer molecules in medical management and better instruments and infra-structural facilities the outcome of mucor treatment has taken a paradigm shift.

Covid 19 is here to stay. We need to find out ways and means to live with it. Be Safe. Take Care!

Friends,

I have considered important recommendations issued by ICMR; Fungal Infection Study Forum (FISF); Indian Journal of Ophthalmology; Expert Committee of Civil Hospital, Ahmedabad; Study Group, Sir Ganga Ram Hospital, New Delhi; from time to time while compiling these guidelines.

Regards!

Dr. Prashant Nikhade

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District Task Force, Nagpur, Maharashtra