

RHINO ORBITO-CEREBRAL MUCORMYCOSIS PREVENTION AND TREATMENT GUIDELINES IN COVID-19 PANDEMIC- AN E.N.T. PERSPECTIVE

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SOURCE OF MUCORMYCOSIS

Mucormycosis (sometimes called zygomycosis) is a serious fungal infection caused by a group of moulds called mucormycetes. These fungi live throughout the environment, particularly in soil and in decaying organic matter, such as leaves, compost piles, or rotten wood. People get mucormycosis by coming in contact with the fungal spores in the environment. For example, the lung or sinus forms of the infection can occur after someone breathes in spores. (1)

IMPORTANT POINTS

- Most patients in early stage do not know that they have the disease, progression is very rapid hence high degree of suspicion is needed to diagnose
- All nondiabetics must also be evaluated for mucormycosis as some patients are being diagnosed with diabetic for the first time during or after Covid infection.
- Early diagnosis of Cases is important for treatment and better outcomes.
- Rational Use of STEROIDS is most important prevention
- Proper Glycemic Control

HIGH RISK PATIENT GROUP: (1)

- Covid patients with Diabetes mellitus
- Most importantly high and uncontrolled diabetes.
- Patients receiving steroids as a part of their Covid-19 treatment are at risk.
- Patients who have received immuno-modulatory drugs e.g. Tocilizumab.

- Previously immunocompromised patients on cancer treatment or with autoimmune conditions.
- Patients on steroids for other medical conditions.
- Patients on Ventilators and on long term Oxygen therapy.
- Patient with solid organ transplant.
- Patients with impaired Renal functions or Renal failure
- Patients with Neutropenia (low number of white blood cells)
- Too much iron in the body (iron overload or hemochromatosis)

NOTE: High degree of suspicion should be maintained in all Covid -19 patients as some patients are diagnosed with Diabetes during Covid infection.

PREVENTION: (2)

Currently, there are no proven feasible measures for prevention and early detection is the best policy in treatment.

Some basic points to remember are:

- Proper control of DM/Sugar
- Judicious use of Steroids. Strict diabetic control during steroid therapy and after recovery
- Low threshold for Antifungals in at risk patients, local wash or systemic therapy
- Tubing of oxygen should be changed frequently and not to be reused
- Humidification of Oxygen and frequent changing of humidifier solution
- Regular gargle by Saline and douching with

- Betadine solution
- Frequent post recovery evaluation and patient education for the disease for early diagnosis
- Avoid water-damaged areas, foods that have spoiled and construction or excavation sites.
- Wear a mask. Fungi may be present in the environment but wearing a mask can keep you from inhaling spores.
- Keep your home environment fungus and spore-free. Clean your refrigerator and pantry regularly and dispose of spoiling foods without delay.
- Boost your immune system and don't take unnecessary risks if you are immunocompromised have an underlying disease or have had a surgery or transplant recently.
- Keep a track of your health and focus on keeping your blood sugar, blood pressure, weight and cholesterol under control.

SIGNS AND SYMPTOMS (2)

- Nasal Crusting and Blood stained nasal Discharge,
- Facial pain, Headache
- Unilateral facial swelling
- Nasal obstruction, Nasal sinus congestion
- Eye Swelling (Proptosis), Eyelid swelling, Vision loss, Diplopia, Restricted eye movement, retro-orbital pain, Ptosis.
- Palatal discoloration, loosening tooth, Discoloration of Face and nose.
- Black lesions on nasal bridge or upper inside of mouth that quickly become more severe
- Blood stained nasal discharge with or without fever.

DIAGNOSIS (2) Early diagnosis of mucormycosis is of utmost importance, since it may improve outcome.

- Early referral to an ENT specialist must be done as soon as we suspect mucormycosis.
- Nasal Endoscopy- Showing Blackening of Middle Turbinate and other nasal structures
- KOH wet mount (deep nasal)
- Tissue for Fungal Culture and sensitivity removed after surgery

- Contrast MRI PNS and Orbit
- Contrast CT PNS
- Blood tests like the 1,3-beta-D-glucan assay and galactomannan assay are not useful in mucormycosis as these proteins are not present in them
- Unproven diagnostic tools
 - a) PCR-based techniques on histological specimens
 - b) Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry can be used to identify the causative species from culture specimens

To guide appropriate drug distribution and rational management of patients with ROCM, the following diagnostic categories should be used:

1. Possible ROCM

- Typical symptoms and signs in appropriate clinical setting as defined above
- No supportive evidence on diagnostic nasal endoscopy and/or GAD-MRI/CT scan

2. Probable ROCM

- Clinical supportive evidence, plus
- supportive evidence on diagnostic nasal endoscopy and/or GAD-MRI/CT scan
- NO evidence on direct microscopy or culture or histopathology with special stains or molecular diagnostics

3. Definite ROCM

- Clinical supportive evidence, plus
- Supportive evidence on diagnostic nasal endoscopy and/or GAD-MRI/CT scan plus
- Confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics

TREATMENT: Note: Currently there is no vaccine for mucormycosis

Currently a 3 pronged approach is recommended for treating mucormycosis

1. Surgical debridement
2. Antifungal therapy along with supportive medical therapy
3. Elimination or control of predisposing factors.

SURGERY: (3) Is done by an experienced ENT

Specialist Endoscopically (mostly). Aggressive surgical debridement of dead tissue still bleeding happens (to be ascertained by MRI /CT non contrast areas) should be considered as soon as the diagnosis of any form of mucormycosis is suspected. It improves both morbidity and mortality. Tissue to be sent for Fungal Culture and sensitivity in Normal Saline

Note: In case of suspected or overt Ocular involvement – an Urgent Ophthalmologist Opinion is needed.

PROPHYLACTIC ANTIFUNGAL THERAPY (4)

Current ICMR guidelines do not recommend any antifungal prophylaxis.

ANTIFUNGAL THERAPY – PROVEN

MUCORMYCOSIS: (5/6)

Three antifungal agents are commercially available for treatment of mucormycosis, namely:

1. Amphotericin B
2. Isavuconazole and
3. Posaconazole

1. Amphotericin B (Liposomal) (7/8)

Preparations: Liposomal preparations available as lyophilized powder form.

Common brands: Ambisome, Phosome, Amphotret, Amphonex, Ampholyn, Amfy, Fungisome; all are available as 50 mg vials. Dosage: Starting dose of 5 mg/kg/day, can increase to 10 mg/kg/day depending on response

Administration: Given through intravenous (IV) route.

Premedication: IV fluid 0.9% NS 500 ml over 3-4 hours followed by injection paracetamol 500 mg IV and injection pheniramine maleate 2 ml (45 mg) IV 30 minutes prior to Amphotericin B infusion.

- ✓ Reconstitute with 12 ml of sterile water yielding a 4 mg/ml solution; dilute using D5 with 3 times the reconstituted volume to get a solution with 1 mg/ml concentration. Intravenous line must be flushed with D5 prior to infusion. Administered by intravenous infusion over a 120 min (reduced to 60 minutes if well-tolerated) which can be increased if

reaction occurs

Side effects:

- i. Infusion related reactions (up to 25%): Chills, rash, pruritus, fever. Managed with temporary stoppage of the infusion, premedication, decreasing infusion rate (give over 2 hours or longer).
- ii. Electrolyte disturbances: Hypokalemia, hypomagnesaemia, hypocalcemia, hypervolemia
- iii. Nephrotoxicity
- iv. Bone marrow suppression – if given over prolonged durations.

Monitoring:

- i. Monitor temperature, input and output and signs of hypokalemia
- ii. Frequent monitoring of renal functions and electrolytes (Cr, Na, K, Mg)
- iii. Monitor CBC, LFTs at baseline
- iv. ECG monitoring if electrolyte disturbances present (hypokalemia)

Other available Amphotericin B:

- Amphotericin B Lipid complex: dose - 5 mg/kg/day
- Amphotericin B deoxycholate: dose - 1.5 mg/kg/day

Manufacturer instructions for these 2 preparations in the package leaflet to be followed.

1. Isavuconazole

Preparations: Oral tablets, intravenous (IV) reconstituted solutions

Common brands: Cresemba (oral and IV)

Dosage: Isavuconazole 200 mg (oral or IV) thrice a day for 6 doses followed by once a day.

Administration:

- a. Intravenous: Infuse over a minimum of 1 hour. Flush line with NS or D5 before and after infusion. Do not administer as an IV bolus injection. Do not mix or infuse with other medications.

Loading dose (Vial)

The recommended loading dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total).

Maintenance dose

The recommended maintenance dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) once

daily, starting 12 to 24 hours after the last loading dose.

Duration of therapy should be determined by the clinical response

- b. Oral: Administer with or without food. For patients able to take orally, ingest capsules whole without crushing. For patients on Ryle tube (RT) feeding, the capsules can be opened, and contents mixed with feed for administration via RT.

Note: No dose adjustments required in Elderly / Hepatic / Renal impairments.

Side effects:

- i. GI side effects - nausea, vomiting, and diarrhea in up to 28% patients.
- ii. Hepatic enzymes elevation seen in 16%; avoid in Child Class C cirrhosis.

Monitoring:

- i. Hypersensitivity reactions with initial doses.
- ii. LFTs at baseline and periodically during therapy.

2. Posaconazole

Preparations: Delayed release tablets, oral suspension, intravenous (IV) solution
Common brands: Noxafil (Oral suspension), Poshope, Picasa (Injection and oral suspension), Posatral, Critposa (injection)

Dosage: Delayed release tablet and IV preparations are equivalent and preferred to oral suspension.

Delayed-release tablet (oral): 300 mg twice daily for 2 doses, then 300 mg once daily

Suspension: 200 mg 4 times daily or 400 mg twice daily

Intravenous: 300 mg twice daily for 2 doses, then 300 mg once daily

Administration:

Suspension: Shake well before use. Administer during or within 20 minutes following a full meal or an oral liquid nutritional supplement or acidic carbonated beverage.

Delayed-release tablet (oral): Swallow tablets whole; do not divide, crush, dissolve, or chew. Administer with food. For patients on Ryle tube (RT) feeding, the capsules can be opened, and contents mixed with feed for administration via RT.

Intravenous: Do not administer IV push or bolus.

Infuse over 90 minutes via a central venous line. Infusion through a peripheral line should only be used as a one-time infusion over 30 minutes in a patient who will be receiving a central venous line for subsequent doses.

Side effects:

- i. Thrombophlebitis - up to 60% with peripheral venous catheter
- ii. Rash and pruritus
- iii. GI intolerance: nausea, diarrhea, vomiting
- iv. Hepatic enzyme elevation

Monitoring:

- i. Hepatic function prior to initiation and during treatment.
- ii. Renal function, especially in patients on IV therapy if eGFR <50 ml/minute/1.73 m²; serum electrolytes (eg, calcium, magnesium, sodium, potassium) prior to initiation and during therapy.
- iii. *Therapeutic drug monitoring*: Timing of concentrations: Obtain trough after steady state has been reached (>7 days after therapy initiation [steady state usually occurs between 7 and 10 days for the oral suspension and at 6 days for the delayed-release tablet and IV solution]).

Recommended trough range:

- a. Prophylaxis: Target trough concentrations >0.7 mcg/ml or >0.9 mcg/ml may be considered when using the delayed release tablet or IV formulation.
- b. Treatment: Target trough concentrations >0.7 mcg/ml and increase to >1.25 mcg/ml if response is poor or ≥1.8 mcg/ml may be considered when using the delayed release tablet or IV formulation

Duration of therapy:

- i. Induction phase: With either Injection Amphotericin B (at least 2 weeks) or Isavuconazole for 2 weeks
- ii. Maintenance/Step down therapy: Once surgical debridement done and patient clinically improving:
 - a. Switch over to Posaconazole or Isavuconazole.
 - b. Given for at least 3 months.
 - c. May required prolonged treatment if immunosuppressed state persists.

Salvage therapy — Use of posaconazole or isavuconazole as salvage therapy for patients who do not respond to or cannot tolerate Amphotericin B

MANAGEMENT OF PEDIATRIC MUCORMYCOSIS

(9)

Primary: Surgical debridement is generally necessary

Antifungal: Liposomal Amphotericin B

- 5 mg/kg IV daily with consideration of escalation to a maximum of 10 mg/kg daily in patients with progressive or extensive disease or possible CNS disease
- Combination therapy should be discussed with ID Consultant
- Options for step-down therapy, salvage therapy, or in patients unable to take LAmB include isavuconazole or posaconazole.
- Please note that voriconazole as it is not active against mucormycosis
- Duration
Generally prolonged (months) until resolution of clinical signs and symptoms or treatment limiting adverse effects
- Therapeutic Drug Monitoring
Therapeutic drug monitoring is recommended for isavuconazole and posaconazole. Please see recommendations for Therapeutic Drug Monitoring of Antifungal Agents

CONTROL OF PREDISPOSING FACTORS

1. Proper Control of Sugars
2. Look for proper control of electrolyte disturbance and Renal function test
3. Control of other mentioned predisposing features

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