Circular

Please find enclosed the State Level COVID Clinical team recommendation in the time of COVID-19 Screening Diagnosis & Management of Mucormycosis that needs to be taken in pursuant.

Mucormycosis is a fungal disease caused by fungi of order Mucorales and class Zygomycetes. It is notorious in causing angioinvasive fungal infection. Due to the difficulties in establishing a definitive diagnosis, many patients will be empirically treated for mucormycosis because they have risk factors for infection and positive cultures and/or compatible clinical syndromes. Intravenous (IV) amphotericin B is the drug of choice for initial therapy. Posaconazole or isavuconazole is used as step-down therapy for patients who have responded to amphotericin B. Posaconazole or isavuconazole can also be used as salvage therapy for patients who don’t respond to or cannot tolerate amphotericin B; for salvage therapy, the decision to use oral or IV posaconazole or isavuconazole depends on how ill the patient is, whether an initial course of amphotericin B was able to be administered, and whether the patient has a functioning gastrointestinal (GI) tract.

The treatment protocol of Covid-19 infection is evolving continuously. The State COVID clinical team has revised the recommendation of Ivermectin in Covid-19 infection:

- Tab Ivermectin 12 mg once a day (200 mcg/kg) for 3 days to be taken in empty stomach (1 hour before or 2 hours after meal).
- Avoid in pregnant and lactating women

The committee also deliberated on the role of Doxycycline in Covid-19 infection and recommends not to include Doxycycline in Covid-19 treatment protocol. However, the use of Doxycycline should be continued for other medical indications in patients of Covid-19 (superadded bacterial infection).
Endst. No. As above Dated Shimla-9 the
Copy for information to:

1. Secretary (Health) to the Govt. of Himachal Pradesh.
2. All the Deputy Commissioners, Himachal Pradesh.
3. Director Health Services, Himachal Pradesh.
4. Director Medical Education & Research, Himachal Pradesh.
5. All the Chief Medical Officer, Himachal Pradesh.
6. All Nodal Officers, DCCC/DCHC/DCH in Himachal Pradesh.
7. All the District Surveillance Officers in Himachal Pradesh.
8. State COVID Clinical Team, Himachal Pradesh.
9. COVID Clinical Committees of all the Medical Colleges of HP.

Mission Director
National Health Mission
Himachal Pradesh
Minutes of the meeting of State COVID Clinical Committee held on 17/05/2021 at 02.00 P.M regarding the incidences of mucormycosis in the Covid-19 patients reported from various parts of the country.

ADVISORY IN THE TIME OF COVID-19:
Screening, Diagnosis & Management of Mucormycosis

Mucormycosis is a fungal disease caused by fungi of order Mucorales and class Zygomycetes. It is notorious in causing angioinvasive fungal infection. The disease is being reported at an alarming frequency over the past decades from India. Indian mucormycosis has certain unique features. Rhino-orbito-cerebral presentation associated with uncontrolled diabetes is the predominant characteristic. Isolated renal mucormycosis has emerged as a new clinical entity. High risk groups include Diabetes mellitus, diabetic ketoacidosis, steroid, cytotoxic drug therapy, HIV, immunosuppressive therapy, malignancy or haematological disorder including iron overload states. It mainly affects people who are on medication for other problems that impairs immunity. Sinuses or lungs of such individuals get affected after fungal spores are inhaled from the air. Suspected Mucormycosis requires urgent intervention, because of the often rapidly progressive and destructive nature of the infection. Delayed initiation of therapy is associated with increased mortality. Maximising survival rates requires rapid diagnostic and therapeutic intervention, including immediate involvement of a multidisciplinary team. Overall mortality: Pulmonary Mucormycosis: 50-70%, Rhinocerebral: 30-70%, CNS involvement: >80%, Disseminated: >90%, AIDS: almost 100%.

Reasons for surge in Covid-19 infection:

- Covid-19 infection has a tendency to worsen diabetes and also precipitate diabetes in previously normal individuals.
- Covid-19 infection may lead to development of Leukopenia and Lymphopenia
- Immunosuppressive treatments such as steroids and IL-6 inhibitors are being widely used in Covid-19 patients
- Underlying chronic respiratory disease
- Intubation /mechanical ventilation
- Coexistence of Covid-19 infection with high blood sugar levels and immunosuppressive treatments would expectedly increase incidence and severity of Mucormycosis
- Mucormycosis may occur during covid-19 infection but mainly occur in the post-Covid follow up phase

**Risk factors:**
- Uncontrolled diabetes mellitus
- Immunosuppression by steroids
- Prolonged ICU stay
- Co-morbidities – post transplant/malignancy
- Voriconazole therapy

**Checklist of sentinel signs and symptoms to be monitored in admitted Covid-19 patients or post-Covid follow up:**

1. Nose and sinuses Mucor infection (relatively early disease). Early detection at this stage can enable early treatment and minimize complications.
   - Headache and nasal obstruction especially if persistent and severe and not responding to pain medicines
   - Nasal crusting and nasal discharges which could be brownish or blood tinged
   - Pain or loss of sensation over face
   - Discoloration of skin of face/localised facial puffinace
   - Loosening of teeth/discoloration or ulceration of palate or bridge of nose
   - Erythematous to violaceous to black necrotic eschar in nasal cavity

**Intraoral findings:**

Halitosis/ Intraoral pus discharge/ Ulceration & Blackening of mucosa/ Exposed palatal bone/ Sinus tract/ Loosening of teeth/ unhealed tooth socket/ Mobility of
maxilla

2. Eye/orbital Mucor infection (Moderately advanced disease).
   - Eye swelling or redness, double vision, loss of vision, eye pain, drooping eyelid
   - Chemosis/ Exophthalmos (Proptosis)/ ophthalmoplegia
   - Discoloration of skin of face/localised facial puffinace
   - Loosening of teeth/discholoration or ulceration of palate or bridge of nose

3. Intracranial Mucor infection (Very advanced disease).
   - II-VI cranial nerve palsies (cavernous sinus involvement): signs of MCA thrombosis

Specific points to be observed in history:

- H/o COVID infection (Immunosuppressive drugs/ Ventilatory care, etc.)
- Co morbid conditions: Diabetes mellitus/ Malignancy/ HIV/ Chronic kidney disease / Obesity/ Other systemic illness
- Local factors (H/O tooth extraction or any other oral/surgical procedure/ Head injury)

Investigations:

- Laboratory Investigations: CBC, ESR, FBS, PPBS, HbA1C, LFT, RFT with electrolytes, HIV, HbSAg, CSF (if indicated)
- Nasal endoscopic examination (if available): Black necrotic eschar tissue
- Radiographic Examination: X- Ray PNS and OPG may be normal
- Contrast enhanced CT scan with 3D Reconstruction findings and MRI with contrast for assessment of disease extent
- Biopsy: Oral cavity: Biopsy from deeper portion of extracted tooth socket/exposed
bone

- **Nasal Cavity**: Nasal endoscopy and crust sampling
- Direct microscopy of bronchoalveolar lavage & transbronchial biopsy

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample to be collected in</th>
<th>To Diagnose</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOH</td>
<td>Saline</td>
<td>Presence of Fungi</td>
</tr>
<tr>
<td>Fungal Culture</td>
<td>Saline</td>
<td>Type of Fungi</td>
</tr>
<tr>
<td>Histopathology</td>
<td>10% Formalin</td>
<td>Fungus/Bony lesions/malignancy</td>
</tr>
<tr>
<td>Frozen section</td>
<td>Saline</td>
<td>Extension of disease/fungus intraoperatively if available</td>
</tr>
<tr>
<td>Squash &amp; imprint cytology preparation</td>
<td>Saline</td>
<td>Presence of fungi</td>
</tr>
</tbody>
</table>

Radiological signs in early phases may be subtle and minimal and may not show florid sinusitis and bone erosions. Lack of these signs does not exclude the diagnosis. Serum tests, such as the 1,3-beta-D-glucan assay and the *Aspergillus* galactomannan assay, are being used with increased frequency in patients suspected of having an invasive fungal infection. The agents of mucormycosis do **not** share these cell wall components and neither test is positive in patients with mucormycosis.

**Treatment:**

Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. Elimination of predisposing factors for infection, such as hyperglycemia, metabolic acidosis, immunosuppressive drugs, and neutropenia, is also
critical. Due to the difficulties in establishing a definitive diagnosis, many patients will be empirically treated for mucormycosis because they have risk factors for infection and positive cultures and/or compatible clinical syndromes. Intravenous (IV) amphotericin B is the drug of choice for initial therapy. Posaconazole or isavuconazole is used as step-down therapy for patients who have responded to amphotericin B. Posaconazole or isavuconazole can also be used as salvage therapy for patients who don't respond to or cannot tolerate amphotericin B; for salvage therapy, the decision to use oral or IV posaconazole or isavuconazole depends on how ill the patient is, whether an initial course of amphotericin B was able to be administered, and whether the patient has a functioning gastrointestinal (GI) tract.

**Medical management:**

1. Mucormycosis should be treated with Injectable antifungal Amphotericin-B for 2-3 weeks on clinical suspicion & as per severity even while awaiting diagnostic and culture reports.
2. Duration of pre operative Amphotericin therapy may be considered as per clinical severity and early need for surgical intervention.
3. Oral antifungal: Overlap with Injectable for 3-4 days before step down and to be continued 1 week after endoscopic biopsy is negative.
4. Liposomal Aamphotericin-B is preferred in cases having renal complication due to Amphotericin-B and in case of cerebral parenchymal involvement.

**First line antifungal therapy: Inj Amphotericin B Deoxycholate (C-AmB):**

- Dose: 1.0-1.5 mg/kg once per day, IV: infused over 4 - 6 hours
- Half-life: Biphasic: Initial 15 to 48 hr, Terminal 15 days
- Disadvantages: Highly toxic, poor CNS penetration
- Install peripherally inserted central catheter (PICC line)
- Pre-infusion administration of 500 to 1,000 mL of normal saline
To avoid infusion-related immediate reactions:

- Premedicate with NSAID and/or Diphenhydramine or
- Acetaminophen with Diphenhydramine or
- Hydrocortisone
- Pre-infusion administration of 500 to 1,000 mL of normal saline

Dosing:

- Renal Impairment: Daily total dose can be decreased by 50% or the dose can be given every other day
- Haemodialysis or CRRT: No dosage adjustment
- Hepatic Impairment: No dosage adjustment
- Watch for: Urine output, Renal function Test (Blood Urea, Serum Creatinine, Electrolytes)

Inj Liposomal amphotericin B (LAmB):

- Dosage: 5 mg/kg per day and in CNS Mucormycosis, the dose is 7.5–10 mg/kg per day
- Advantages: Less nephrotoxic, better CNS penetration than AmB or ABLC
- Disadvantage: Expensive
- Contraindication: Hypersensitivity

Inj Amphotericin B lipid complex (ABLC):

Dosages: 5 mg/kg/day -

Advantages and Supporting Studies: Less nephrotoxic than AmB deoxycholate
Disadvantage: Expensive, Possibly less efficacious than LAmB for CNS infection

Second line- AZOLE Derivatives (Step Down or Salvage Therapy):

Step-down therapy: Posaconazole and Isavuconazole are broad-spectrum azoles that are available in both parenteral and oral formulations. For patients who have responded to Amphotericin B, Posaconazole or Isavuconazole can be used for oral step-down therapy.
Amphotericin B should be continued until the patient has shown signs of improvement; this usually takes several weeks.

**Salvage therapy:** Posaconazole or Isavuconazole may be used as salvage therapy for patients who do not respond to or cannot tolerate Amphotericin B. The IV formulation of Posaconazole or Isavuconazole should be used in patients who have to be switched from Amphotericin B before they have had a favorable response and in patients who have an inability to absorb oral medications.

**A. Isavuconazole:**
Isavuconazole should be given as a loading dose of 200 mg (equivalent to 372 mg of the prodrug isavuconazonium sulfate) IV or orally every 8 hours for the first six doses followed by 200 mg IV or orally every 24 hours thereafter. Because the IV formulation of isavuconazole is highly water soluble and does not contain the SBECVD vehicle, there are no known concerns about administering the IV formulation to patients with renal impairment.

**B. Posaconazole:**
Dosage: Posaconazole (both IV and delayed-release formulations) is given as a loading dose of 300 mg every 12 hours on the first day, followed by a maintenance dose of 300 mg every 24 hours thereafter. Oral formulation should be taken with food. The IV formulation should be avoided in patients with moderate or severe renal impairment (creatinine clearance [CrCl] <50 mL/minute) due to the potential for accumulation of the betadex sulfobutyl ether sodium (SBECVD) vehicle, unless an assessment of the possible benefits and risks to the patient justifies its use. If it is used in patients with renal impairment, serum creatinine should be monitored closely, and, if increases occur, consideration should be given to changing to the extended-release tablet formulation of posaconazole or to IV or oral isavuconazole. Oral suspension of posaconazole is not preferred since it is not highly bioavailable and requires fatty food for absorption.
**Combination therapy:**

There are no convincing data to support any form of combination antifungal therapy, and combination therapy is not recommended in the major treatment guidelines. Larger studies are needed to establish whether combination therapy is beneficial.

a. Lipid polyenes (both ABLC and L AmB) plus echinocandins (e.g. caspofungin, micafungin, and anidulafungin) :- Improves survival rate among disseminated mucormycosis including CNS disease. Better outcome than monotherapy with polyenes.

b. Lipid polyenes plus azole (Posaconazole or Isavuconazole)

c. Triple therapy (Lipid polyene plus echinocandin plus azole)

**Duration of therapy:**

Patients can be switched from Amphotericin B to delayed-release Posaconazole or Isavuconazole tablets for oral step-down therapy once a favourable clinical response has been achieved, which usually takes several weeks. Therapy should continue until there is clinical resolution of the signs and symptoms of infection, as well as resolution of radiographic signs of active disease; therapy should also continue until reversal of underlying immunosuppression has been achieved, when feasible. Therapy often extends for months, and some patients remain on therapy for life if immunosuppression cannot be corrected. Treatment duration is a personalized decision. Regular follow up should be ensured initially monthly for 3 months then SOS. Monitor patients clinically and with radiography for response and to detect disease progression.

**Surgery:** Aggressive surgical debridement of involved tissues should be considered as soon as the diagnosis of any form of Mucormycosis is suspected. Surgical intervention with removal of necrotic tissue and debulking infection has been associated with improved survival in anecdotal clinical reviews of rhinocerebral and pulmonary infection.

**Prevention:**

- Control hyperglycemia
- Monitor blood glucose level post COVID-19 discharge and also in diabetics
- Use steroid judiciously observing correct timing, correct dose and duration
- Use antibiotics/antifungals judiciously
• Use masks if you are visiting dusty construction sites
• Wear shoes, long trousers, long sleeve shirts and gloves while handling soil (gardening), moss or manure

**Humidifiers:**
• Use clean, sterile water for humidifiers during oxygen therapy
• Never use un-boiled tap water nor mineral water
• Change the water in the humidifier daily
• Humidifier should be washed in mild soapy water, rinsed with clean water and dried in air before reuse
• Fill up to about 10 mm below the maximum fill line
• Do not let the water level pass below the minimal fill line
• Once a week, all the components of humidifier should be soaked in mild antiseptic solution for thirty minutes, rinsed in clean water and dried in air

**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 & microscopy, culture), for detecting fungal aetiology
• Do not lose crucial time to initiate treatment for mucormycosis

**Recommendation:**
1. To constitute a multispecialty clinical team for surveillance and early diagnosis of Mucormycosis at DCH level. The team should consist of following specialty/superspecialty
   • Otolaryngorhinology
   • Ophthalmology
   • Oral and Maxillofacial surgeon
   • Plastic surgeon/Neurosurgery if not available, then Surgeon
2. Rational use of steroids (to avoid high dose for longer duration)
3. Adequate control of Diabetes Mellitus in patients on steroids
4. Every DCH should procure adequate Amphotericin-B stock

References:

3. ICMR EVIDENCE BASED ADVISORY IN THE TIME OF COVID-19 (Screening, Diagnosis & Management of Mucormycosis)

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To not include Doxycycline in Covid-19 treatment protocol. However, the use of Doxycycline should be continued for other medical indications in patients of Covid-19 (superadded bacterial infection).

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