KGMU Guidelines for the prevention and management of COVID-19-associated Rhino-Orbito-Cerebral Mucormycosis (C-ROCM)

- **Scope**
  - All 'COVID-19 positives' or 'post-COVID-19 patients' suspected of or diagnosed with COVID-19 associated Mucormycosis. This document has been prepared with special focus on COVID-19 associated Rhino-Orbito-Cerebral Mucormycosis (C-ROCM). Post-COVID-19 state shall be defined as 4 weeks from the date of being RT-PCR negative (or equivalent laboratory estimation, or clinical criteria constituted by 3 days without fever and any other symptom)

- **Objectives**
  - Prevention of C-ROCM
  - Early detection of C-ROCM
  - Management of C-ROCM based on:
    - Severity of disease
    - Rational use of medications

- **Susceptible population (High-risk patients)**
  - Diabetics, especially uncontrolled or with ketosis
  - Those on mechanical ventilation, especially for 2-3 weeks
  - Those on high dose steroids or on any dose for >2-3 weeks
  - High cytokines (IL6), high ferritin
  - Voriconazole therapy
  - Use of Deferoxamine or other iron overloading therapies
  - Those with high CT scores (higher disease severity)
  - Immunocompromised (HIV, organ transplantation, etc.) or on immunosuppression medication (azathioprine, mycophenolate mofetil, etc.)
  - Neutropenic individuals (ANC <1500)
  - Autoimmune disorders

- **Target associations obtained from previous Mucormycosis-related outbreaks**
  - Use of dirty linen, contaminated linen shelves and dirty bins (Duffy et al, 2014, New Orleans, Cutaneous variety, Rhizopus delemar)
  - Environmental/weather changes (Tornado): Necrotizing cutaneous mucormycosis caused by Apophysomyces trapeziformis after receiving puncture wounds caused by flying debris during a tornado (Neblett et al, 2012, Missouri) **[Not applicable in the current scenario]**
  - Contaminated air handling units and ventilation ducts (El-Mahallawy et al, 2016, Egypt, Rhizopus)
  - CDC Investigations: Water line damage, Hospital construction contaminating the patient care areas, improper air filtration; contamination by dust and debris of patient management units by patient's attendants or HCP appears less common
  - The shift from aspergillus to mucormycetes due to increasing use of voriconazole prophylaxis in highly immunocompromised patients (Benedict et al, 2017, Lancet Infect Dis)
  - Negative pressure isolation rooms (Novosad et al, 2016, Pennsylvania)

- Water leak (wall dampness leading to accumulation of fungus) (Hancock-Allen et al, 2016, Colorado)
- Hospital construction; dust and moisture (Patterson et al, 2016)
- 2012, Fungal outbreak in US associated with compounding drugs (MPS-related): The index case had Aspergillus fumigatus meningitis; subsequent patients had Exserohilum rostratum; **[No Mucormycosis was detected]**
- Fungal contamination of nebulizer devices (Peckham et al, 2016, UK, Rhizopus; Aspergillus was most frequently isolated fungus)

- **Prevention of C-ROCM based on target associations:**
  - **Good general practices:**
    - No tubes (hydration, nebulization, ventilation), masks (Hudson, NRM, NIV) or prongs to be reused.
    - Common use equipment viz. nebulizers, BiPaP machines and Ventilatory units, must follow a standard decontamination process when changeover is done **[Discussion]**
    - It is advised that *only distilled water* is used for the purpose of hydration.
    - If distilled water is not available, it should be ensured that water used for hydration of oxygen delivery, steam inhalation or ventilation delivery unit is clean; *refilling should be done only after clearing and cleaning of the residua in the jar.*
    - Prevention of use of contaminated linen
    - Regulations required to prevent contamination of patient-care areas (not alone ICUs or HDUs) by dust, dampness, water leakage, etc. **[More inputs can come with decontamination and sanitization practices]**
    - Monitoring of passages (leading to patient-care areas) and AHU
    - Monitored use of antibiotics (broad-spectrum vs based on antibiogram) and antifungals (voriconazole, fluconazole) **[More elaboration required]**
    - Use of masks by the patients even in the treatment units, especially those with negative pressure.
  - **Appropriate glycemic control with regular monitoring to prevent hyperglycemia and ketosis**
  - **Judicious use of steroids**
    - NO steroids to be given to those with SpO2 is >94% or those who do NOT require supplemental oxygen (CDC Protocol)
    - Singular use, especially in the first 5-7 days, without an anti-viral cover must be discouraged/condemned
    - Dexamethasone: 6mg/day for 10 days (WHO Protocol); follow this regime until otherwise required
    - High dose steroids use should be reserved for specialists or those trained in handling these patients
  - **Weekly nasal endoscopy by the ENT surgeon of all earmarked as high-risk for C-ROCM**

- **For early detection of Mucormycosis symptom-based severity assessment of COVID-19 or post-COVID-19 patients suspected of C-ROCM should be done:** **Honavar, 2021**
    - ***Stage 1:*** **Involvement of nasal mucosa**
        - Nasal stuffiness, nasal discharge, foul smell, epistaxis
    - ***Stage 2:*** **Involvement of paranasal sinuses**
        - Stage 1 symptoms, plus
        - Facial pain, facial edema, dental pain, systemic symptoms (fever, malaise)
    - ***Stage 3:*** **Involvement of orbit**
        - Stage 1 and/or 2 symptoms, plus
        - Pain in and around the eye, proptosis, diplopia, diminution or loss of vision, facial paraesthesia or anesthesia (infraorbital nerve, V1, V2 nerve distributions)
    - ***Stage 4:*** **Involvement of the CNS**
        - Stage 1, 2 and/or 3 symptoms, plus
        - Bilateral proptosis, focal neurological deficit, altered consciousness, seizures

- **To guide appropriate stage-wise management of C-ROCM according to the stage the following proposed staging of C-ROCM may be used:** **Honavar, 2021**
    - ***Stage 1: Involvement of nasal mucosa***
        - 1a: Limited to the middle turbinate
        - 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct
        - 1c: Involvement of the nasal septum
        - 1d: Bilateral nasal mucosal involvement
    - ***Stage 2: Involvement of paranasal sinuses***
        - 2a: One sinus
        - 2b: Two ipsilateral sinuses
        - 2c: >two ipsilateral sinuses and/or palate/oral cavity
        - 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible
    - ***Stage 3: Involvement of the orbit***
        - 3a: Nasolacrimal duct, medial orbit, vision unaffected
        - 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected
        - 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, diminution or loss of vision
        - 3d: Bilateral orbital involvement
    - ***Stage 4: Involvement of the CNS***
        - 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate
        - 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis
        - 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction
        - 4d: Multifocal or diffuse CNS disease

- **Diagnosis of mucormycosis: Laboratory aspects**
    - Confirmation on direct microscopy (KOH mount) or culture or histopathology with special stains or molecular diagnostics
    - Specimen required:

Disease	Acceptable Specimen	Acceptable specimen in Emergency situation	Unacceptable specimen
Rhinocerebral mucormycosis	Nasal scrapings from necrotic areas/ Nasal crust from necrotic areas/ Biopsy from affected areas in STERILE Universal containers containing sterile saline. (**To be collected by ENT specialist)** **If only ocular involvement, without nasal involvement is seen, a high nasal swab may be acceptable.**	High Nasal swabs (to be sent only in emergency situations when ENT services are not available)	Dry nasal swabs Leaky containers
Pulmonary mucormycosis	Sputum, Bronchial brush washing/ broncho-alveolar lavage (BAL)/ Lung biopsy- Collected by bronchoscope, Fluoroscope guided trans-thoracic needle aspiration or open lung biopsy specimen	Same as acceptable specimen	Saliva
Cutaneous mucormycosis	Biopsy specimen taken from centre of the lesion including subcutaneous fat (moulds frequently invade blood vessels of the dermis and sub cutis, resulting in an ischemic cone at the skin surface) Pus aspirate (from abscess) Transported in Universal container	Pus aspirate (from abscess) Transported in Universal container	Swab from lesion
Gastrointestinal mucormycosis	Biopsy from affected area in sterile saline in universal container	Same as acceptable sample	Stool, Gastric aspirate
Renal mucormycosis	Biopsy in sterile saline in universal container	Same as acceptable sample	Urine

    - **Test requisition label:** KOH microscopy & culture (C-ROCM)
    - **Transportation of sample**
        - All specimens should be transported to the lab preferably within 2 hours of sample collection.
        - DO NOT FREEZE the sample
        - DO NOT CRUSH / HOMOGENISE the biopsied material
        - Transport the specimen at room temperature to the PRO (Central sample collection centre Room no. 6) between 9 AM to 2 PM. From 2 PM-9 AM transport the samples to the Virology lab (COVID sample receiving area). **[Revise it to designate a laboratory for the purpose of evaluation]**
    - **Turnaround time**
        - KOH Microscopy report: 4 hours

        - Fungal Culture report: 2 to 21 days
    - **Serology**
        - Non-contributory
        - Galactomannan, 1,3 β D-glucan may be done to ***rule out*** concomitant or disguised Aspergillosis

- **Diagnosis of mucormycosis: Imaging preference**
    - Computed Tomography (CT) of the paranasal sinuses and orbits with contrast: Best used to look for bony erosion
    - MRI of the brain and orbit with Gadolinium contrast: Best to look for soft tissue and the extent of involvement

- **To guide appropriate drug distribution and rational management of patients with C-ROCM, the following diagnostic categories should be used:**
    - ***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*
    - ***Probable ROCM***
        - Clinical supportive evidence, *plus*
        - Supportive diagnostic nasal endoscopy and/or GAD-MRI/CT scan
        - *No evidence on direct microscopy or culture or histopathology with special stains or molecular diagnostics*
    - ***Definite ROCM***
        - Clinical supportive evidence, *plus*
        - Supportive diagnostic nasal endoscopy and/or GAD-MRI/CT scan, *plus*
        - Confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics

- **Rational use of Amphotericin B**
    - ***Preparations available:***
        - Amphotericin B deoxycholate (AMB-D)
        - Lipid-complex Amphotericin B (AMB-LC)
        - Liposomal Amphotericin B (AMB-L)
            - Most preferred AMB due to a lower incidence of nephrotoxicity, higher tissue penetrability and higher tissue concentration
            - First line AMB provided the supply logistics are favourable

    - ***Where to use AMB-L preferably?***
        - Category ≥3b (Diffuse Orbital involvement with preserved vision)
        - Pulmonary
        - Disseminated

    - ***Logical use of AMB-D***
        - GFR >60 mL/min

        - <1.5-fold rise in creatinine from baseline within 7 days of initiation of AMB-D
        - If D-AMB is well tolerated, use it for a minimum for 2 weeks, upto 4 weeks, before stepping down.

    - ***Indications for changing from AMB-D to AMB-L or AMB-LC:***
        - GFR 30-59 mL/min, or
        - ≥1.5-fold rise in creatinine from baseline within 7 days of initiation of AMB-D

    - ***Indications of early step-down therapy to Isavuconazole or Posaconazole (before 4 weeks of any AMB)***
        - If any AMB is not tolerated, or
        - GFR <30 ml/min, or
        - Unavailability of any AMB

- **Use of anti-seizure medication:**
    - Either of Levetiracetam or Lacosamide may be used as they have minimal drug interactions and are available in intravenous as well as per-oral forms.
    - Levetiracetam:
        - Upto 16yrs: Start with 10mg/kg q12h; can increase q2w to 30mg/kg q12h
        - >16yrs: 500mg q12h; can increase q2w to 1500mg q12h
    - Lacosamide:
        - Upto 50kg: Start with 1mg/kg q12h; can increase q1w to 2-4mg/kg q12h
        - >50kg: 50mg q12h; can increase q1w to 100-200mg q12h
    - If LFTs are deranged prefer Levetiracetam; if KFTs are deranged prefer Lacosamide

- **Steps in seeking specialty reference:**
    - **Step 1:** Suspicion of C-ROCM based on clinical features; check for any baseline imaging
    - **Step 2:** Seek ENT consultation for examination and Nasal Endoscopy
        - With positive findings, send sample for laboratory confirmation
        - No contributory findings: Follow clinically and reassess at 72 hours
    - **Step 3:** Get the imaging done, if not done previously
        - MRI-GAD to be preferred over CT in order to get a better idea of soft-tissue involvement
    - **Step 4:** All confirmed or highly suspected cases to be notified
    - **Step 5:** Based on stage, further consultations from Ophthalmology, Oral & Maxillofacial surgery and Neurosurgery/Neurology to be done
    - **Step 6:** Start medical management, as defined in the Algorithm, pending laboratory confirmation in 'Probable' cases (not in 'Possible' cases) and while surgical management is being planned (if applicable)
    - **Step 7:** Follow-up protocol with the Medical Team