ಕರ್ನಾಟಕ ಸರ್ಕಾರ

ಸಂಖ್ಯೆ: ಆಕುಕ 181 ಅಮುಕಾ 2021

ಕರ್ನಾಟಕ ಸರ್ಕಾರ ಸಚಿವಾಲಯ
ವಿಕಾಸ ಸೌಧ
ಬೆಂಗಳೂರು, ದಿನಾಂಕ: 26.05.2021

ಪರಿಷ್ಕೃತ ಸುತ್ತೋಲೆ

ವಿಷಯ: ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್ ಸೋಂಕಿನ ಚಿಕಿತ್ಸೆ ಹಾಗೂ ನಿರ್ವಹಣೆ ಕುರಿತಂತೆ ಕ್ಲಿನಿಕಲ್ ತಜ್ಞರ ಪರಿಷ್ಕೃತ ಶಿಫಾರಸ್ಸುಗಳನ್ನು ಅನುಸರಿಸುವ ಬಗ್ಗೆ.

ಉಲ್ಲೇಖ: ಸುತ್ತೋಲೆ ಸಂಖ್ಯೆ: ಆಕುಕ 163 ಅಮುಕಾ 2021, ದಿನಾಂಕ: 18.5.2021

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ಕೋವಿಡ್-19 ಸೋಂಕಿಗೆ ಸಂಬಂಧಪಟ್ಟ ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್ (ಬ್ಲಾಕ್ ಫಂಗಸ್) ಸೋಂಕಿನ ಚಿಕಿತ್ಸೆ ಹಾಗೂ ನಿರ್ವಹಣೆ ಕುರಿತಂತೆ ಉಲ್ಲೇಖದನ್ವಯ ಚಿಕಿತ್ಸಾ ವಿಧಾನಗಳನ್ನು ಈಗಾಗಲೇ ರಾಜ್ಯದ ಎಲ್ಲಾ ಆಸ್ಪತ್ರೆಗಳಲ್ಲಿ ಅನುಸರಿಸಲು ಸೂಚಿಸಲಾಗಿತ್ತು.

ಮುಂದುವರೆದು, ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್ ಸೋಂಕಿನ ಚಿಕಿತ್ಸೆ ಹಾಗೂ ನಿರ್ವಹಣೆ ಕುರಿತಂತೆ ರಾಜೀವ್ ಗಾಂಧಿ ಆರೋಗ್ಯ ವಿಶ್ವವಿದ್ಯಾಲಯದ ಕ್ಲಿನಿಕಲ್ ತಜ್ಞರ ಸಮಿತಿಯ ಪರಿಷ್ಕೃತ ಶಿಫಾರಸ್ಸುಗಳನ್ನು (Revised Recommendations of Clinical Expert Committee) ಈ ಸುತ್ತೋಲೆಯೊಂದಿಗೆ ಲಗತ್ತಿಸಿದ್ದು, ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್ ಸೋಂಕಿಗೆ ಚಿಕಿತ್ಸೆ ನೀಡುವ ಆಸ್ಪತ್ರೆಗಳಲ್ಲಿ ಕಡ್ಡಾಯವಾಗಿ ಪಾಲಿಸುವುದು.

ಅದೇ ಅಲ್ಲದೇ, ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್ ಸೋಂಕು ಬರದಂತೆ ತಡೆಗಟ್ಟಲು ಕೋವಿಡ್ 19 ಸೋಂಕಿಗೆ ಚಿಕಿತ್ಸೆ ನೀಡುವ ಸಂದರ್ಭದಲ್ಲಿ ರೋಗಿಯ ವೈಯಕ್ತಿಕ ಸ್ವಚ್ಛತೆಯ ಪಾಲನೆಯ ಜೊತೆಗೆ ಇತರ ಪೂರಕ ಕ್ರಮಗಳನ್ನು ಪಾಲಿಸುವುದೂ ಸಹ ಅಗತ್ಯವಾಗಿದೆ. ಅವುಗಳೆಂದರೆ, ಸ್ವಚ್ಛವಾದ ಮಾಸ್ಕ್ ಹಾಗೂ ಪಿಪಿಇ ಕಿಟ್‌ಗಳ ಬಳಕೆ, ಭಾರತ ಸರ್ಕಾರ ಹಾಗೂ ಕರ್ನಾಟಕ ಸರ್ಕಾರವು ನಿಗದಿ ಪಡಿಸಿರುವ ಚಿಕಿತ್ಸಾ ಶಿಷ್ಟಾಚಾರದ ಕಡ್ಡಾಯ ಪಾಲನೆ, ಸ್ಟಿರಾಯ್ಡ್‌ಗಳ ವಿವೇಚನಾಯುತ ಬಳಕೆ, ಆಕ್ಸಿಜನ್ ಸಿಲಿಂಡರ್, ಪೈಪಿಂಗ್ ಹಾಗೂ ವೆಂಟಿಲೇಟರ್ ಸರ್ಕ್ಯೂಟ್‌ನ ಸ್ವಚ್ಛತೆ ಮತ್ತು ಹ್ಯೂಮಿಡಿಫೈಯರ್ ನಲ್ಲಿ ಸಾಮಾನ್ಯ ಲವಣಯುಕ್ತ (normal saline) ಬಳಕೆಯು ಅವಶ್ಯವಾಗಿದೆ. ಕೋವಿಡ್ ಆಸ್ಪತ್ರೆಯ ಆವರಣದಲ್ಲಿ ಯಾವುದೇ ಕಾಮಗಾರಿಗಳನ್ನು ಕೈಗೊಳ್ಳದಿರುವುದು, ಕೋವಿಡ್ ವಾರ್ಡ್‌ನ ಒಳಗೆ ರೋಗಿಯ ಸಂಬಂಧಿಕರ ಓಡಾಟವನ್ನು ನಿರ್ಬಂಧಿಸುವುದು ಹಾಗೂ ಪ್ರತಿ ಶಿಫ್ಟ್‌ನಲ್ಲಿಯೂ ಸೋಂಕುನಿವಾರಕ ದ್ರಾವಣದಿಂದ ನೆಲದ ಸ್ವಚ್ಛತೆ, ರೋಗಿಯ ಸುತ್ತ-ಮುತ್ತ ಸ್ವಚ್ಛಗೊಳಿಸುವುದನ್ನು ಖಚಿತಪಡಿಸಿಕೊಳ್ಳತಕ್ಕದ್ದು.

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ಕೋವಿಡ್‌ನಿಂದ ಗುಣಮುಖನಾದ ವ್ಯಕ್ತಿಯು ಆಸ್ಪತ್ರೆಯಿಂದ ಡಿಸ್‌ಚಾರ್ಜ್ ಹೊಂದುವ ಸಂದರ್ಭದಲ್ಲಿ ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್ ಲಕ್ಷಣಗಳ ಕುರಿತು ಮಾಹಿತಿ ನೀಡಬೇಕು. ಇವುಗಳ ಜೊತೆಗೆ , ಸೌಮ್ಯ ಸ್ವರೂಪದ ಲಕ್ಷಣಗಳಿದ್ದರೂ ಸಹ ಸ್ವಯಂ ವೈದ್ಯ ಪದ್ಧತಿಯನ್ನು (Self Medication) ಪಾಲಿಸದೆ, ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್‌ನ ಲಕ್ಷಣಗಳು ಕಂಡುಬಂದ ತಕ್ಷಣವೇ ವೈದ್ಯರ ಸಲಹೆಗಳನ್ನು ಪಡೆದು ಪಾಲಿಸುವುದು. ಅನಿಯಂತ್ರಿತ ಮಧುಮೇಹ, ಇತರ ಆರೋಗ್ಯ ಸಮಸ್ಯೆಗಳು, ಇಮ್ಯುನೋಕಾಂಪ್ರಮೈಸ್ಡ್ ಲಕ್ಷಣಗಳಿದ್ದಲ್ಲಿ ಕಡ್ಡಾಯವಾಗಿ ವೈದ್ಯರಿಗೆ ಮಾಹಿತಿ ನೀಡುವುದು, ಇತ್ಯಾದಿ ವಿಷಯಗಳ ಕುರಿತು ಸಲಹೆಯನ್ನು ನೀಡತಕ್ಕದ್ದು.

ಮ್ಯುಕೋರ್ ಮೈಕೋಸಿಸ್ ಸೋಂಕಿನ ಚಿಕಿತ್ಸೆ ಹಾಗೂ ಸಮಗ್ರ ನಿರ್ವಹಣೆಯ ಹಿನ್ನೆಲೆಯಲ್ಲಿ ಈ ಎಲ್ಲಾ ಅಂಶಗಳ ಪಾಲನೆಯನ್ನು ಖಚಿತಪಡಿಸಿಕೊಳ್ಳಲು ಸೂಚಿಸಿದೆ.

(ಜಾವೇದ್ ಅಖ್ತರ್)
ಸರ್ಕಾರದ ಅಪರ ಮುಖ್ಯ ಕಾರ್ಯದರ್ಶಿ
ಆರೋಗ್ಯ ಮತ್ತು ಕುಟುಂಬ ಕಲ್ಯಾಣ ಇಲಾಖೆ

ಇವರಿಗೆ :

1. ಸರ್ಕಾರದ ಪ್ರಧಾನ ಕಾರ್ಯದರ್ಶಿಗಳು, ವೈದ್ಯಕೀಯ ಶಿಕ್ಷಣ ಇಲಾಖೆ
2. ಮುಖ್ಯ ಆಯುಕ್ತರು, ಬಿ ಬಿ ಎಂ ಪಿ, ಬೆಂಗಳೂರು
3. ಎಲ್ಲಾ ಜಿಲ್ಲೆಯ ಜಿಲ್ಲಾಧಿಕಾರಿಗಳು,
4. ಎಲ್ಲಾ ಜಿಲ್ಲೆಗಳ ಮುಖ್ಯ ಕಾರ್ಯನಿರ್ವಹಣಾಧಿಕಾರಿಗಳು,
5. ವಿಶೇಷ ಆಯುಕ್ತರು, ಬಿ ಬಿ ಎಂ ಪಿ, ಬೆಂಗಳೂರು
6. ಜಿಲ್ಲಾ ಆರೋಗ್ಯಾಧಿಕಾರಿಗಳು/ ಜಿಲ್ಲಾ ಸರ್ಜನರು/ಆಡಳಿತ ವೈದ್ಯಾಧಿಕಾರಿಗಳು/ ತಾಲ್ಲೂಕು ವೈದ್ಯಾಧಿಕಾರಿಗಳು ಹಾಗೂ ಎಲ್ಲಾ ಸಾರ್ವಜನಿಕ ಆಸ್ಪತ್ರೆಗಳ ವೈದ್ಯಕೀಯ ಅಧೀಕ್ಷಕರು.
7. ಜಿಲ್ಲಾ ಸರ್ವೇಕ್ಷಣಾಧಿಕಾರಿಗಳು, ಎಲ್ಲಾ ಜಿಲ್ಲೆಗಳು
8. ಮುಖ್ಯ ಆರೋಗ್ಯಾಧಿಕಾರಿಗಳು, ಬಿ ಬಿ ಎಂ ಪಿ, ಬೆಂಗಳೂರು.

ಪ್ರತಿಯನ್ನು ಮಾಹಿತಿಗಾಗಿ :

1. ಮುಖ್ಯ ಕಾರ್ಯದರ್ಶಿಯವರು, ಕರ್ನಾಟಕ
2. ಆಯುಕ್ತರು, ಆರೋಗ್ಯ ಮತ್ತು ಕುಟುಂಬ ಕಲ್ಯಾಣ ಸೇವೆಗಳು, ಬೆಂಗಳೂರು.
3. ಅಭಿಯಾನ ನಿರ್ದೇಶಕರು, ಎನ್ ಹೆಚ್ ಎಂ, ಬೆಂಗಳೂರು.
4. ನಿರ್ದೇಶಕರು, ಆರೋಗ್ಯ ಮತ್ತು ಕುಟುಂಬ ಕಲ್ಯಾಣ ಸೇವೆಗಳು, ಬೆಂಗಳೂರು.
5. ನಿರ್ದೇಶಕರು, ವೈದ್ಯಕೀಯ ಶಿಕ್ಷಣ, ಬೆಂಗಳೂರು.
6. ಮಾನ್ಯ ಆರೋಗ್ಯ ಮತ್ತು ಕುಟುಂಬ ಕಲ್ಯಾಣ ಹಾಗೂ ವೈದ್ಯಕೀಯ ಶಿಕ್ಷಣ ಸಚಿವರ ಆಪ್ತ ಕಾರ್ಯದರ್ಶಿ
7. ಕಚೇರಿ ಪ್ರತಿ.

COVID-19 ASSOCIATED MUCORMYCOSIS

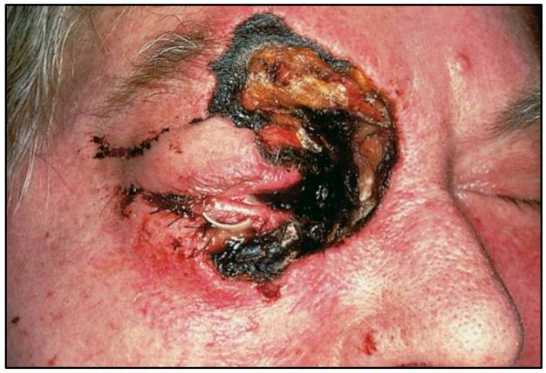
COVID-19 continues to be a significant problem worldwide. While several treatment options have been evaluated, systemic glucocorticoids have been shown to improve survival in COVID-19. Unfortunately, the irrational use of glucocorticoids can lead to secondary bacterial or fungal infections.

MUCORMYCOSIS is a rare, non-contagious fungal infection that mainly affects people who are on steroids for COVID-19, one of the life-saving treatments for severe and critically ill Covid-19 patients. Steroids reduce inflammation and appear to help stop some of the damage that can happen when the body's immune system goes into overdrive to fight off corona virus. But they also reduce immunity and push up blood sugar levels. This drop in immunity could be triggering these cases of Mucormycosis. When fungal spores are inhaled from the air, it invades the sinus and makes its way into the lungs, intra-orbital and intracranial regions. This has a high morbidity and overall mortality rate of 50%.

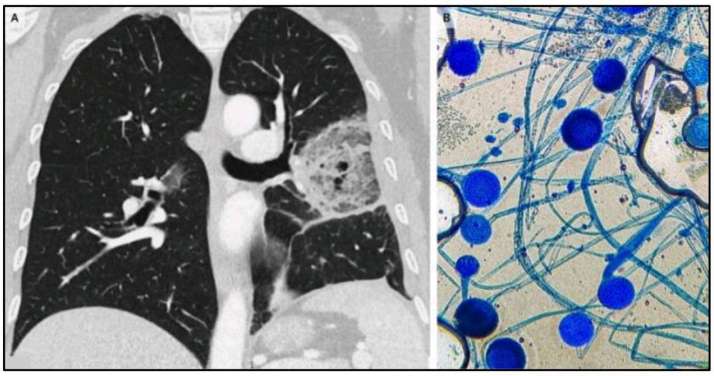
COVID19 Associated Mucormycosis can occur with active COVID-19 infection **(concomitant)** and can occur sequentially in weeks or months following recovery **(sequential).**

COVID19 Associated Mucormycosis based on clinical presentation is classified as:

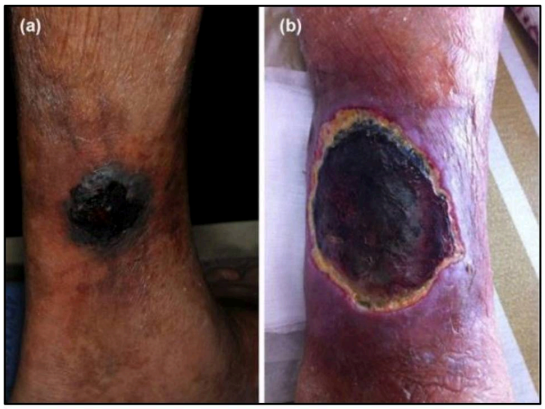
1. Rhino-orbito-cerebral Mucormycosis (ROCM): -
   most common in people with uncontrolled diabetes, Post-kidney transplant
2. Pulmonary Mucormycosis: -
   most common in people with cancer, organ transplant or a stem cell transplant
3. Gastrointestinal Mucormycosis: -
   more common among young children 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



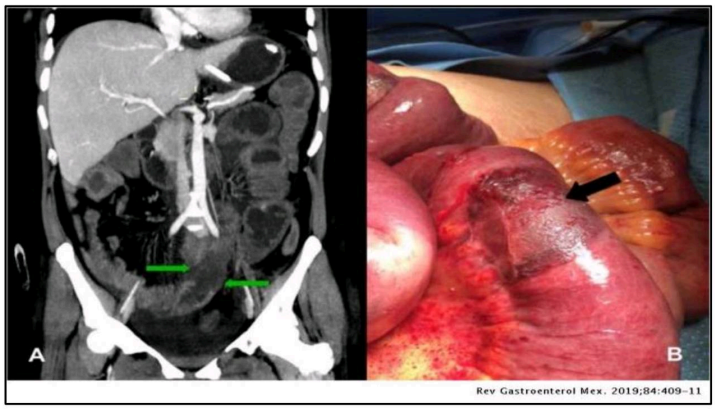
Rhino Orbital Cerebral Mucormycosis.



Pulmonary Mucormycosis.



Cutaneous Mucormycosis.



Gastrointestinal Mucormycosis.

Symptoms and Signs:

- 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.

Predisposing factors are:

- Uncontrolled diabetes mellitus
- Immunosuppression by steroids/immunomodulator drugs.
- Prolonged ICU stays
- Co-morbidities – Post Transplant/malignancy/Sickle Cell Anemia
- Voriconazole therapy

When to suspect:

- 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 symptoms.

Diagnosis

Mucormycosis is a medical emergency and in correct context should be started on empirical therapy even prior to diagnostic confirmation. Suspected patients should undergo appropriate radio-imaging study at the earliest. MRI/CT-PNS with brain contrast study for ROCM and plain CT thorax for pulmonary involvement must be done.
Diagnosis is confirmed by fungal staining/culture from the sample collected.

Direct Microscopy:

- KOH staining/ Calcofluor Staining/ Lactophenol Cotton Blue Staining /PAS stain
- non-septate/ pauci-septate hyphae with Right/ obtuse Angled Branching.
- ribbon-like hyphae (at least 6–16 μm wide) with Sporangium at terminal ends
- Vessel occlusion

Culture:

- Specimens should not be grounded so that viability is preserved
- **Routine media at 30°C and 37°C:**
  Typical findings: cottony white or greyish black colony.
  Also Test for Susceptibility.
- Rapid Growth on Sabouraud Dextrose Agar and Potato Dextrose Agar: 3-7 days

HPE:

- To differentiate mucor from other moulds
- To look for Angioinvasion.

Radiology:

- Diffuse infiltration partly surrounded by a thick, wall-like consolidation**: the reversed halo sign.**
- Multiple nodular infiltrates

- Pleural effusion +/-
- Hypointense sign on Magnetic resonance imaging, T1 weighted, a central hypo intensity in a lung consolidation or nodule, corresponding to a central area of necrosis caused by vascular obstruction with secondary lung infarction and sequestration.
- MRI shows pulmonary nodule with central hypo intensity in right upper lobe, corresponding to a central area of necrosis caused by vascular obstruction with secondary lung infarct and sequestration
  Black Turbinate Sign,
  Cavernous sinus Thrombosis.
  Infratemporal fossa involvement.
- **Vascular occlusion sign** on CT angiography, defined as interrupted vessel at the border of a focal lesion without depiction of the vessel inside the lesion or peripheral to the lesion
- CT PNS: nodular thickening of sinus linings, absence of fluid levels, and spotty destruction of bony walls of the sinuses & Infiltration of the peri antral fat planes.
  Erosion and thinning of hard tissues, Enlargement of masticatory muscle, Mucosal thickening of tissues.
- Repeated Negative Galactomannan and Beta-D glucan tests
- BAL Fluid Microscopy if the facility is available.
- Transbronchial biopsy/ CT guided biopsy from lung if the facility is available.

Molecular Identification:

- Semi-nested qPCR, HRM, Multiplex Target: 18s, ITS, 28s or rDNA
- Immunohistochemical staining

Treatment:

Since it affects various parts of the body, treatment requires a **Multidisciplinary team** of microbiologists, internal medicine specialists, intensivist neurologists, ENT specialists, ophthalmologists, dentists, surgeons and others.

- Control diabetes and diabetic ketoacidosis
- Reduce steroids (if patient is still on) with aim to discontinue rapidly
- Discontinue immunomodulating drugs
- No antifungal prophylaxis needed
- Extensive Surgical Debridement - to remove all necrotic materials
- Medical Management.

Medical treatment:

Amphotericin B is the drug of Choice for Mucormycosis. However, alternately Posaconazole or Isavuconazole can also be used.

a. Install peripherally inserted central catheter (PICC line)
b. Maintain adequate systemic hydration to reduce renal toxicity and hypokalemia.

c. Infuse Normal saline IV before Amphotericin B infusion
d. Antifungal Therapy, for at least 4-6 weeks.
e. Monitor patients clinically and with radio-imaging for response and to detect disease progression

Liposomal AMPHOTERICIN-B:

Background: Amphotericin B (Amp-B) is an antifungal which has been used in improving the outcomes in Mucormycosis. There are many clinical trials/ guidelines indicating that Amphotericin-B is the drug of choice for Mucormycosis.

Preferred: Liposomal Amphotericin B - 5-10mg/Kg/day intravenous as infusion in 5% dextrose over two to three hours, once daily.

Reconstitution: 12 ml of sterile water (NOT NORMAL SALINE) is mixed with the vial to yield 4 mg/ml of the preparation. This is shaken vigorously for 30 seconds to disperse the content and make a yellow translucent solution. This is further diluted in 5% Dextrose to produce a 0.5-2 mg/ml suspension. A 5-micron filter is provided with the syringe – the contents are injected via this filter to the 5% Dextrose. The filter must be used only ONCE for one vial. An in-line membrane filter must be used for IV infusion.

In case of non-availability of Liposomal Amphotericin B,

- **Lyophilized amphotericin-B (Conventional)** can be used.
- Test dose: 1mg in 100ml D5 over 20 mins.
- Dosage not exceeding 1.5mg/kg/day as IV infusion in 500mL D5 over 3-4 hours- monitor Platelet counts and renal functions while administering Amp-B.
- It is contraindicated in patients with renal injury- Acute Kidney Injury.
- Lyophilized Amp-B can be used in Chronic Kidney Disease patients who are on dialysis (as the drug is dialysable).
- Monitoring of Urine output, Electrolytes (especially potassium) & Renal Function Test is a must.

Duration: Amphotericin-B to be continued for 4-6 weeks.

After 4-6 weeks of Amphotericin B therapy, **Consolidation phase** by Posaconazole (oral) till clinical improvement and radiological clearance.

Criteria to be fulfilled for dispensing Amphotericin-B Injection: Patient should fulfil the below-listed criteria:

1. Clinical symptoms and signs of Mucormycosis supported by clinical picture(photo) and Histopathological examination or PCR confirming the diagnosis of Mucormycosis.

   and either of below
2. Patients who are undergoing treatment for COVID-19
3. Covid-19 infection in last 3 weeks

Exclusion criteria for Amphotericin B:

Patient intolerant/allergic to Amphotericin B. (In such individuals, Isavoconazole/ Posaconazole can be used).

- Posaconazole
    - Oral: Loading dose 300mg BD, f/b 300mg OD for 4-6 weeks
    - Given with Food to enhance absorption
    - Delayed-release tablets may be used if available.
    - It is expensive with a single tablet costing Rs. 400.
    - Check Posaconazole trough level after 7 days of therapy & avoid interacting drugs.
- Isavuconazole
    - Intravenous: 300mg TID on day 1&2, f/b 300mg OD from day 3.
    - Oral :200mg three time a day for two days, followed by 200mg once a day.
    - has the added advantage of shortening the QT interval which may have been affected by HCQ, Azithromycin which many patients still continue to receive.
    - Requires 7-8 days to achieve therapeutic concentrations. Hence measure the levels in the blood after a week of initiation of therapy.
    - Absorption maximized when taken with high fat food.

Surgical Management:

The aim is to remove all necrotic materials. The procedure must be done at the earliest. The optimal time of surgery to reduce the operative risk to the patient with COVID-19 and the risk of transmission to the operating team is a contentious issue.

Surgical management also provide sample for HPE and Microbiological Diagnostics.

Surgery:

Functional Endoscopic Sinus Surgery (FESS) + Exenteration/debridement.

Alternatives to Polyenes (AmB) in treating Mucormycosis

- Specific to species causing Mucormycosis:

    -Isavuconazole

    -Deferasirox (mixed evidence Spellberg et al. (2012), DEFEAT Mucor study)

- Other therapies with limited evidence:

    -Immunomodulation: G-CSF, GM-CSF, IFN-γ

    -Cellular therapy: Granulocyte transfusion (GTX), Adoptive T-cell therapy (works with Aspergillus; no evidence for Mucormycosis sp.), Monoclonal antibodies

Treatment Algorithm for Mucormycosis:

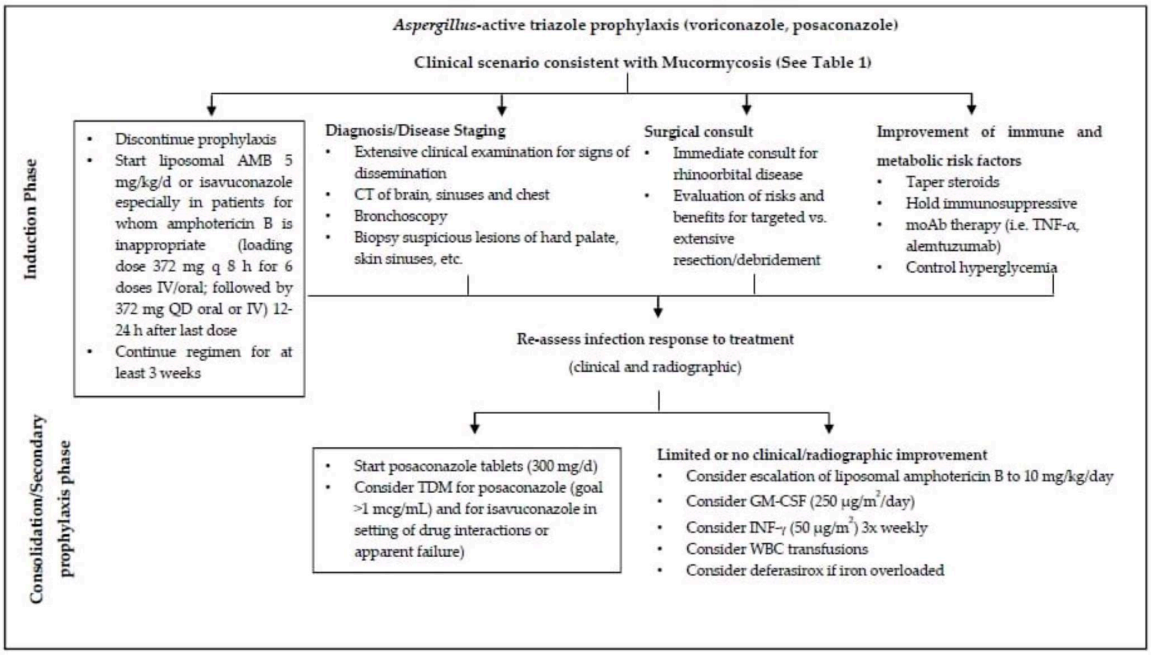


Figure 1. Algorithm for Mucormycosis Treatment. AMB: amphotericin B; CT: computed tomography scan; moAb: monoclonal antibodies; TDM: therapeutic drug monitoring; GM-CSF: granulocyte-macrophage colony stimulating factor; INF-γ: interferon—gamma; WBC: white blood cells.

How can it be prevented?

Prevention of the infection must be the priority in this situation of Resource limited settings of the ongoing pandemic.

- Do not Self-Medicate 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.

- 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 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.

    *As per HICC Guidelines on Infection control aspects of Respiratory therapy equipment/devices, issued by AIIMS-New Delhi, dated 21.05.21 (Enclosed as Annexure1)

- 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 so as 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 so as 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.

Measures must be taken to resolve the hospital level issues in infection control as appropriate.

Annexure 1

Infection Control Aspects of Respiratory Therapy Equipment: *

*As per HICC Guidelines on Infection control aspects of Respiratory therapy equipment/devices, issued by AIIMS-New Delhi, dated 21.05.21

Mechanical Ventilator:

- Surface disinfection of panels, trolleys and support arm to be performed once a day with alcohol-based disinfectant.
- Disposable circuit tubing to be used; these should not be changed routinely unless these are soiled.
- For humidification, preferably use a HME (HME should not be used along with a heated humidifier).
- HME to be changed daily.
- For heated humidifier, use only Sterile water/Distilled water. In reusable humidifier chambers, once the water level falls below the lower mark, one should empty the humidifier and refill with sterile water/ Distilled water; one should not top up.
- Closed suction to be preferably used and changed at least once daily.
- For any further disinfection, follow the manufacturer recommendations.

High Flow Nasal Cannula:

- Surface disinfection of the unit once a day with alcohol-based disinfectant.
- Sterile water/ Distilled water to be used in humidifier bottles.
- Terminal disinfection of the HFNC equipment to be done as recommended by the manufacturer [In AIRVO HFNC- thermal disinfection is recommended by the manufacturer].

Oxygen Concentrators:

- Surface disinfection of the unit once a day with alcohol-based disinfectant
- In humidifier bottle, use sterile water/ Distilled water. Once the water level falls below the lower mark, one should empty the humidifier and refill with Sterile water/ Distilled water; one should not top up.

NIV:

- Surface disinfection of the unit once a day with alcohol-based disinfectant.
- HME filter may be attached to non-vented mask.

Oxygen Humidifier:

- Oxygen humidifier to be disinfected daily.
- In humidifier bottle, use sterile water/ Distilled water. Once the water level falls below the lower mark, one should empty the humidifier bottle and refill with sterile water/ Distilled water, one should not top up.

Suction bottles:

- The bottles should be periodically emptied.
- Every 6 hours, bottles to be cleaned with soap and warm water and dried.
- For disinfection of the tubing's, after every suction, freshly prepared 1% NaOCl (sodium hypochlorite) solution kept ready in appropriate container or bottles, should be suctioned

through the tubings.

Nebulizer Chamber:

- A single nebulizer chamber should be used for a single patient only.
- A fresh circuit should be used for each patient.
- After use, nebulizer should be emptied and dried.

Ultrasonic Nebulizer (E.g., ATOM)

- Surface disinfection of the unit once a day with alcohol-based disinfectant
- Preferably a fresh circuit should be used for each patient.
- The medication chamber should be emptied and dried after every use.
- The water reservoir should be filled with sterile water/ Distilled water and changed every day.

Annexure 2

Directives to Hospitals

- Formulate Mucor Cells in every hospital. This should include ENT surgeon, Pulmonologist, Infectious Disease Control Specialist and an administrative staff. A telephonic helpline must be established in all hospitals
- Infection Control Committees should be set up in all hospitals. This must include one member of the Management, one Microbiologist, one Physician, One Pulmonologist, one Surgeon, one Anaesthesiologist/Intensivist, Nursing Superintendent, Biomedical Chief and Chief of Maintenance and supply.
- This team must meet once a week during an epidemic and once a month during non-epidemic periods
- During an epidemic, the Infection Control Committee is broadly mandated to
    - Maintain a database of the particular disease that will be updated on a daily basis
    - Identifying an outbreak
    - Investigating an outbreak
    - Describing the outbreak
    - Suggesting and testing a hypothesis regarding the source of contamination
    - Control measures and follow-up
    - Communication with hospital staff and public
    - Evaluate the source of infection

- In the present Mucormycosis outbreak
    - Maintain a database of Mucormycosis patients that will be updated on a daily basis that is also made available to the MoHFW. This must include general patient data, demographic data, referral data, clinical symptoms & signs, treatment details, outcome of treatment and possible source of infection. Particularly, it must also include history of COVID 19 in the past, antibiotic use/abuse, steroid use/abuse, use of steam inhalation, Diabetes Mellitus
    - Identify an in-house outbreak and if so, take immediate corrective measures
    - Identify possible sources of Mucor contamination in ER, ICU, OT and wards by microbiological sampling techniques
    - Investigating Gaseous supply chains from the point of entry of cylinders to the point of exit through nasal canulae/masks/nebulisers (that essentially includes all points in the entire gaseous transport chain)
    - Weekly microbiological sampling for Mucormycosis from various points in: OT, ICU, ER, wards, humidifiers, nasal canulae, gaseous outlets, oxygen generating chambers, gas cylinders (both inner and outer surface after use) and various points in air conditioning units.
    - All cylinders and other medical supplies coming into a hospital must be sterilised according to SOPs
    - Close monitoring of sterilization of medical equipment in the hospitals by concerned staff
    - Ensure use of sterile water in humidifiers
    - Ensure strict sterilization of masks, nasal canulae and other gas delivery equipment
    - Medical staff education regarding Mucormycosis
    - Public awareness outreach regarding Mucormycosis
    - All construction activities in and around hospitals must be ceased immediately
    - All air conditioning units in all parts of the hospitals to be serviced and optimized

Community responsibilities in Mucormycosis

- Use masks in a proper way: Do not use masks for many days. 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.

  Avoid frequent touching of masks and face.
- Avoid self-medication with steroids and antibiotics
- Avoid steam inhalation, especially in case of suspected Mucor infections.
- Use O2 concentrators using sterile water. Sterilize the equipment after every use
- Sanitize air conditioning units at home and workplace
- Avoid plants at home
- Ensure that bio waste is not kept inside homes and is disposed-off on a daily basis
- Strictly follow general sanitization protocols like hand sanitization, social distancing, wearing masks, avoiding crowded places
- **Stay away from hospitals and other public places unless when absolutely necessary**

Administrative Measures:

1. Maintain a central database on Mucormycosis, updatable on a real-time basis
2. Call upon all gas (O2 and N2) providers in the state and instruct them to follow strict SOPs for sterilisation as mandated by PESO
3. Random checks to be made at all medical gas manufacturing/supplying units
4. Call upon all PPE/mask manufacturing units and instruct them to follow strict SOPs for sterilisation as mandated by PESO
5. Random checks to be made at all PPE/mask manufacturing units
6. High powered committee to Investigate the hypothesis of contamination of hospitals with Mucor due to the diversion of industrial units to produce medical grade oxygen

Annexure 3

Microbiological Surveillance for Covid associated Mucormycosis in Healthcare settings

Introduction:
In settle plate sampling Petri dishes containing SDA agar medium are opened and exposed for one hour, thus allowing fungal spores deposit onto them. Petri dishes which are 90 mm in diameter are used. The number of fungal spores deposited onto the agar surface of the plate over the period of exposure is ascertained by incubation of the plate and counting the number of fungal colonies, more commonly known as colony forming units (CFU).

Sample locations:
ICU/HDU/ Wards
Preference to be given to areas from where Mucormycosis cases are reported.

Method of sampling:
1. Examine the plates for contamination, prior to use.
2. The person doing the procedure should wear PPE and enter covid ward. 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 may be marked on each plate or recorded separately:
   - date and time of day sample taken
   - area/location of sample
   - position/sample number
3. Keep the plates into the ICU/ HDU/ Ward where they are to be exposed. Four side tables next to beds to be identified so as to ensure it falls within 10 cubic ft (depending on the size of rooms, no of set of plates to be decided, say for every three beds one set of plates can be used assuming 6 feet distance for 2 beds)
4. Place the plates in the appropriate positions with the lids still on.
5. Raise 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 sterile swabs to be labelled appropriately and to be dipped sterile distilled water, excess water to be drained aseptically.

The following items to be swabbed:

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 to 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:

Once received 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 plated 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 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:

The following samples are preferred in the order given below.

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

Should be sent for following investigations:

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 Mucorales.

Annexure 4

Industrial Oxygen vs Medical Oxygen

Industrial Oxygen is a type of oxygen used in industrial settings, like manufacturing plants, for tasks that may include combustion, oxidation and even to help accelerate certain chemical reactions. Industrial oxygen is not intended to be inhaled like medical oxygen is, but rather serves a complementary role to create the actions that are carried out in these facilities. Steelmaking, for instance, is one of the largest users of industrial oxygen.

Some common uses of industrial oxygen include:

- Metal manufacturing, such as in steel production.
- Welding, cutting, flame cleaning, etc.
- Assisting in the creation of certain fuels.
- A bleaching chemical to help create paper and paper-based products.

However, one of the biggest differentiators when it comes to industrial oxygen versus medical oxygen is that industrial oxygen is not safe to breathe. Industrial oxygen can be generated by oil-lubricated, oil-less or oil-free compressors. This will depend on what kind of product is produced using the compressed air application. In fact, purity levels are not safe for human use — not to mention that industrial oxygen could also contain contaminants in the tanks that are absent from medical oxygen tanks based on the stringent FDA regulation of it.

Medical oxygen is a type of oxygen that is used, simply put, for medical purposes. This type of oxygen can only be generated by medical air compressors. Specific government agencies regulate what type of compressor can be used to produce oxygen due to the risk of contamination from an incorrect compressor. Medical compressors generally come in oil-free or oil-less varieties. Medical oxygen is only administered for medical purposes as a life-saving treatment. It may also be used for certain medical procedures, notably if a patient has to go under general anesthesia. Medical oxygen is also typically administered in non-medical situations as well. For example, athletes may take it when training or individuals may undergo oxygen therapy.

However, during the present pandemic situation, due to shortages of availability of Medical grade oxygen, repurposed use of Industrial Oxygen was diverted to the hospitals. Along with this arose the problem of shortage of tankers for transporting the oxygen. As a result, Liquid Nitrogen Gas Tankers have been converted to Liquid Oxygen Tankers, as per the Government of India SOP.

Noting that such conversion inherent risk and against the international practice, the Petroleum and Explosives Safety Organization (PESO) has issued the SOP for the user industry. PESO has said that traditionally the conversion was not agreed by the department to carry and transport liquid Oxygen due to the risks. However, due to extreme emergency requirement to transport liquid Oxygen, the department has issued the following guidelines to be followed to convert the tankers.

SOP for Conversion of used LNG tankers for Oxygen service

Issued by Petroleum and Explosives Safety Organization, Govt of India.
No. D-18019/SOP/Implementation, Dated 04.05.2021

This has reference to suggestions submitted by industries; SOP has been revised accordingly.

Cryogenic transport tank used for transportation of LNG/ has traditionally not been agreed by PESO for their conversion to carrying and transport liquid Oxygen because of its inherent risk and against the international practice.

Due to extreme emergency requirement to transport liquid Oxygen. requests from Industries are received proposing conversion of LNG tanker to Oxygen service. It is informed that there are only 138 Nos. of LNG tankers in the country.

Since, such conversion is not a safe practice and not followed internationally, extreme precaution has to be taken by the applicant for such conversion. The conditions set forth by PESO has to be followed in view of the above extreme exigencies, and following steps to be observed by the user industry:

1. Cryogenic transport tanker shall be warmed up and purged with hydrocarbon free Nitrogen and the discharged purged gas composition shall be monitored till the hydrocarbon vapour concentration is reduced to 0.01%.
2. Inlet of vaporizer coil/pump suction filter and any other points of the system must be examined to ensure absolute absence of hydrocarbon.
3. Conversion shall be undertaken under the supervision of competent and experienced person.
4. Warming of tanker shall initially be taken up with Nitrogen up to the temperature of 15°C using cold Nitrogen and then up to maximum 50°C. Care must be taken to ensure that tanker and associated parts are not exceeding maximum design temperature and with allowable rate of temperature increase.
5. Please ensure that all valves, piping works, filling and sampling hoses and pump assembly are made up to the Oxygen compatible material.
6. Purged gas analysis shall be carried out and samples to be taken for consistent concentration of hydrocarbon vapor less than 1PPM.
7. The completely purged LNG tanker must be used for filling once with liquid Nitrogen to ensure 100% hydrocarbon free vessel and also to ensure that filling and delivery hoses/assembly and faucet adopter are compatible for Oxygen delivery.
8. Level of filling of Nitrogen/Oxygen shall be standardized for level volume/weight and suitable marking or interlock shall be provided.
9. The discharge and receipt of the product shall be replaced with the suitable adapter for Oxygen.

The above protocols are mandatory. PESO shall be informed while deciding LNG tanker for conversion and after completion of the above conditions, a declaration issued by the applicant shall be submitted to PESO for acceptance and issue of commissioning permission to use tanker for Oxygen service.
The authorized signatory shall be solely responsible and confirm in their declaration that above conditions has been complied with.

Annexure 5

COVID SOP PRACTICES FOR MEDICAL GASES

Due to drastic increase in the cases of Mucormycosis and its spread established to the particular use of oxygen in the treatment of patients with COVID19, the unprecedented situation raised an urgency to prepare Standard Operating Procedures (SOP) defining the good manufacturing practices for medical gases and testing protocols guidance manual.

This guideline focuses on the testing protocols to follow during the production and control of medical gases to ensure appropriate quality standards before distribution.

Implement a Quality Management System:

1. Companies involved in the manufacture, control, storage and distribution of medical gases should document and implement a clearly defined quality management system for this purpose.
2. The quality management system should make sure that:
    a. medical gases manufactured are controlled, stored and distributed in accordance with regulations in this document and have passed the quality tests.
    b. arrangements are made for the manufacturer to supply and use correct containers and labels.
    c. there is a system for quality risk management.
    d. calibrations and validations are carried out where necessary.
    e. the finishes product is correctly processed and checked with specifications.
    f. a system in place to handle and investigate complaints, returns, recalls and self - inspection.
    g. deviations and changes are investigated and recorded with appropriate root cause analysis done.
3. The quality management system should cover a systematic process to assess, control, communicate and distribute medical gases and protect the patient from receiving wrong or contaminated product.
4. Personnel involved in the manufacture, control, storage and distribution of medical gases should be appropriately trained especially where activities could influence quality of medical gases and containers, such as maintenance of cylinders.

SOP and Documentation:

5. Specifications, SOP and related documents relating to manufacture, control, storage and distribution of medical gases should be available.
6. Documents should be designed prepared, reviews and distributed with care.
7. Documents should be authorized by appropriate responsible persons.
8. Documents requiring entry of data, should be clear, legible and indelible.
9. Labels on the cylinder should comply with the legislation and contain the minimum information:
    a. name of medical gas.
    b. batch number assigned by the manufacturer.
    c. expiry or use before date.
    d. specific storage conditions and handling precautions.
    e. directions for use.
    f. name and address of the manufacturer.

10. Records should be maintained for reach batch of gas manufactured.
11. In addition, quality records should be available for at least, but not limited to:
    a. equipment.
    b. cleaning and sanitization.
    c. quality and validation test date

Microbiological Testing:

12. The quality management system is responsible for the maintenance of the test reports and ensuring quality.
13. Swab samples should be taken from the cleaned cylinder before re-filling gas to check for fungi growth.
14. Every batch of cylinder before refilling should be disinfected and dried according to PESO guidelines.
15. Swab samples from every tanker before refilling would be tested to check for contaminations.
16. A disinfection kit should be provided with the personnel supplying to clean the outer surfaces for ensuring proper delivery of gases from tanks and cylinder.
17. Swab samples from washed disinfected cylinder and filled cylinder, empty disinfected container before filling would be taken and inoculated in SDA (Sabouraud Dextrose Agar) media at 20-25®C and observed for colony growth and identification.
18. Sampling from each filled batch should be tested at random from one cylinder with colony growth test and quantitative PCR.
19. Records of analysis should be maintained.
20. Records should be maintained for distribution of each bath of medical gas.
21. Every batch of gas should be tested for microbial growth before dispatch.
22. Records of the test report should be maintained and should contain:
    a. name of the medical gas.
    b. batch number.
    c. references to the relevant specifications and testing procedures.
    d. test results and reference to any specifications (limits).
    e. date and reference number of testing.
    f. initials of the person who performed the testing.
    g. date and initials of the persons who verified the testing and calculations where appropriate.
    h. a clear statement of release or rejection and the dated signature of the designated responsible person.
23. Storage areas should be an enclosed area, kept clean and dry with sufficient ventilation.
24. A proper cleaning schedule of storage areas should be available to maintain the sterility of storage cylinders.

Records and Transport

25. Records should be maintained for each batch of gas manufactured. These records should include relevant information such as the following:
    a. name of the product
    b. batch number
    c. identification of the person(s) carrying out each significant step.
    d. equipment used (e.g., filling manifold)
    e. quantity of cylinders/mobile cryogenic vessels before filling, including individual identification references and water capacity(ies)
    f. pre-filling operations performed.

g. key parameters that are needed to ensure correct fill at standard conditions.
h. results of appropriate checks to ensure the containers have been filled.
i. specification of the finished product and the results of quality control tests (including reference to the calibration status of the test equipment).
j. quantity of rejected cylinders/mobile cryogenic vessels, with individual identification 475 references and reasons for rejections.
k. details of any problems or unusual events, and signed authorization for any deviation 477 from instructions.
l. specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment) by the responsible person, date and signature.

26. Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident seal or device. The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.
27. Broken or damaged cylinders should be withdrawn from usable stock.
28. Procedures for transport should ensure that,
    a. the identity of the medical gas is not lost.
    b. there is no risk of contamination of the medical gas.
    c. precautions are taken against damage and theft.
    d. environmental conditions are maintained if required.

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