Special Article

# Anaesthetic Considerations in Rhino-Orbito-Cerebral Mucormycosis

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## Abstract

Rhino-orbito-cerebral mucormycosis is a serious infection that can complicate the course of coronavirus disease 2019 (COVID-19). Surgical debridement of infected/necrotic tissue along with antifungal co-medication constitutes the mainstay of treatment. Amphotericin B can produce electrolyte imbalance and nephrotoxicity. The lungs and other organs can be affected to various extents by COVID-19 infection. Both mask ventilation and intubation can be difficult in these patients. Meticulous preoperative evaluation and optimisation, followed by a carefully planned anaesthetic aimed at maintaining haemodynamic stability, often spells success.

**Keywords:** Airway management, amphotericin B, anaesthesia, coronavirus disease 2019, mucormycosis

## Introduction

Severe acute respiratory syndrome coronavirus 2 is being increasingly associated with fungal co-infections. Although systemic corticosteroids form the mainstay of treatment, they increase the risk of secondary infections such as aspergillosis and mucormycosis. Immune dysregulation caused by the virus itself also predisposes patients to infections.[1] High free iron levels, low oxygen tension, low pH and hyperglycaemia seen in coronavirus disease 2019 (COVID-19) patients also contribute towards mucormycosis infection.[2]

Laboratory investigations for the diagnosis of mucormycosis include direct microscopy, histopathology and polymerase chain reaction.[3-5] Computed tomographic (CT) scan and magnetic resonance imaging (MRI) are used to assess sinus involvement and evaluate contiguous structures such as the brain and eyes.[6] While CT imaging can be rapidly obtained for detecting bony erosions. MRI is useful for detecting intraorbital and intracranial extension and diagnosing soft tissue and vascular involvement [Figures 1 and 2]. The staging system is based on the anatomical progression of rhino-orbito-cerebral mucormycosis (ROCM).[7] There is progressive involvement of nasal mucosa (Stage 1), paranasal sinuses (Stage 2), orbit (Stage 3) and central nervous system (Stage 4).

Effective control of blood sugar, early treatment with amphotericin B and surgery form the mainstay

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of treatment. Isavucunazole and posaconazole are alternatives to liposomal amphotericin B.[8] Other emerging additive treatments under evaluation are hyperbaric oxygen therapy (HBOT), echinocandin and iron chelators.

## Implications of Mucormycosis

ROCM can cause devastating complications that include cranial nerve palsies, loss of vision, palatal perforations, epiglottitis and life-threatening sepsis. Patients in the intensive care unit (ICU) who are bedridden for a long time are at risk of critical illness myopathy and may be at risk of succinylcholine-induced hyperkalemia. In immune-compromised individuals, the infection begins in the alveoli or paranasal sinuses.[9] The hyphae of mucormycosis are angioinvasive, leading to infarction and necrosis of infected tissue.[10] The 30-day mortality rate can nearly double (35% to 66%) with a 6-day delay in treatment.[11] Mucormycosis is a time-sensitive condition necessitating early diagnosis and prompt treatment to avoid morbidity and mortality.

Delaying surgical debridement presuming that antifungals will be sufficient for management can be disastrous. Though surgical debridement is pivotal, precision and technique are important. Depending on the extent of tissue involved, functional endoscopic sinus surgery (FESS), endoscopic medial maxillectomy, partial maxillectomy, total maxillectomy, mandibulectomy, orbital exenteration or craniofacial resection may be indicated [Figure 3]. Total or partial maxillectomy may require a flap which can be performed in a staged manner. FESS usually does not involve major blood loss but maxillectomy might require intraoperative blood transfusion.

### Amphotericin B

In appropriate cases, antifungal treatment is started before surgery to limit the area for debridement. Amphotericin B is the drug of choice for mucormycosis. It has various formulations with lipid-based formulations being less nephrotoxic. Negligible absorption from the gastrointestinal system warrants intravenous administration. The drug is administered through a central line to avoid phlebitis.

Nephrotoxicity may result from any formulation of amphotericin B.[12] Before starting infusion of amphotericin B, volume expansion with 500 mL of 0.9% sodium chloride is known to reduce decrease

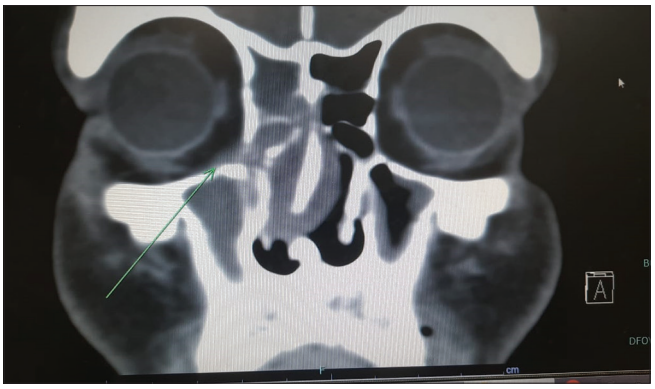

**Figure 1:** Computerised tomographic scan showing breach through the floor of orbit

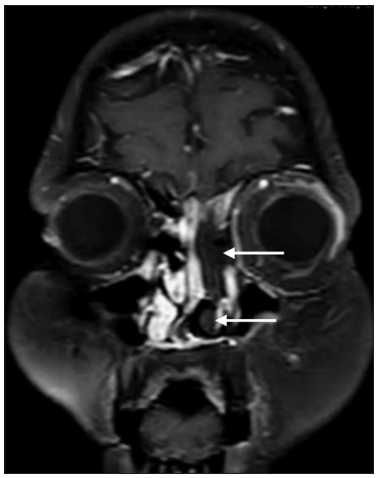

**Figure 2:** Magnetic resonance image showing black turbinate sign of mucor

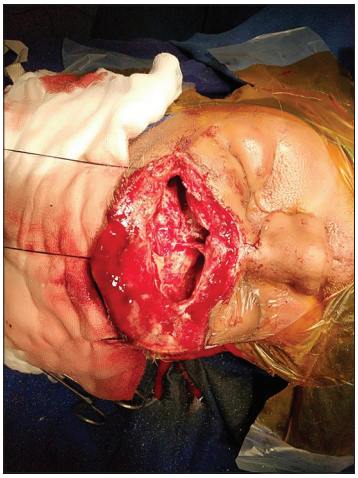

**Figure 3:** Bilateral frontal sinuses opened for debridement

in glomerular filtration rate.[13] However, volume expansion should be done cautiously in patients with decreased ejection fraction or pre-existing renal disease. Important side effects of amphotericin B therapy such as hypokalaemia, hypomagnesemia

and hyperchloraemic acidosis should be closely monitored and corrected before anaesthesia to avoid life-threatening complications.[14]

Anaesthetic management in patients with acute renal failure can be challenging and is associated with high morbidity and mortality. Adequate mean arterial pressure has to be maintained intraoperatively to prevent further renal injury.[14]

## Anaesthetic management

### *Preoperative evaluation*

Evaluation of the COVID status (acute or post-COVID) is essential to plan the extent of personal protective equipment usage as both anaesthesia and surgery are aerosol-generating procedures. If possible, surgery should be postponed till the patient has no active COVID-19 infection. However, this is often not possible as morbidity and mortality are known to increase with delay in treatment. Various co-morbidities of the patient, current clinical status, overall patient fitness and ongoing medications should be evaluated in detail.

COVID-19 is known to be associated with cerebral/pulmonary thrombi, myocarditis, encephalopathy, limb ischaemia and acute kidney injury. These should be actively sought for while evaluating the patient. The severity of COVID-19 infection and its residual effects on the lungs, the extent of oxygen requirement and ventilator assistance, and use of drugs such as steroids, blood thinners, antivirals and immunosuppressants should be noted.[15]

High-resolution CT of lungs helps in assessing the extent of lung damage. Other investigations required are complete blood count, blood sugar, renal and liver function tests, electrocardiogram, 2D echocardiography and chest X-ray. In sick patients, arterial blood gas analysis is essential. Depending on the type of surgery and associated co-morbidities, blood transfusion might be required preoperatively and adequate blood should be reserved as per surgical requirements. Blood sugar should be controlled with insulin infusion if needed. Antiplatelets and other anticoagulants started in the ICU should be withheld if possible. Emergency surgeries can be done under the cover of blood products. Lateral canthotomy and inferior cantholysis for orbital decompression may be needed to save the eye.[16] Oxygen saturation on room air should be noted.

Rhino-orbital-cerebral mucormycosis often involves the palate, orbit and brain resulting in pronounced clinical symptoms. Thorough physical examination of the face and mouth in these patients is essential to prevent last-minute surprises on the operation table. Facial structure and oral cavity should be examined for oedema, bone destruction, palatal perforation, loose teeth and frail tissue. These can lead to difficult mask holding and/or difficult intubation. Laboratory and clinical parameters should be optimised to the best extent that time permits.

### *Intraoperative management*

Intravenous access can be difficult. If required, a central venous catheter and an arterial line should be placed. There are some reservations about placing the central venous catheter in the internal jugular vein due to its proximity to the site of infection.[17,18] Subclavian or femoral vein is preferred in such circumstances. As antifungal treatment is for a prolonged period, it is preferable to insert a central venous catheter or a peripherally inserted central catheter if not already done while the patient is still in the operating room.

Both mask ventilation and intubation can be difficult in these patients.[17] In severe cases, fungal debris at the laryngeal inlet, palatal perforation and glottic oedema can lead to difficult intubation.[19] Palatal obturators can decrease intraoral space and make laryngoscopy difficult [Figure 4]. Dislodgement of palatal obturators can obstruct the airway during mask ventilation.[19] Videolaryngoscopes can be helpful for such intubations.[19] A difficult airway cart should be readily available. The need for a tracheostomy should

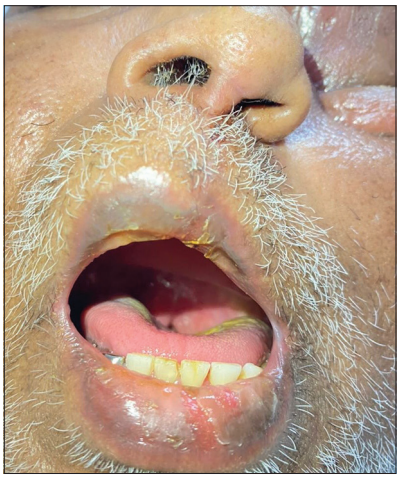

**Figure 4:** Obturator and decreased mouth opening after left maxillectomy

be discussed in advance with the otorhinolaryngologist. Intubation should be quick as these patients are prone to rapid desaturation.

Depending on the preoperative lung condition, mechanical ventilation should be 'lung protective', aiming for plateau pressures between 25 and 30 cm $H_2O$. Fluid management should be based on requirements and renal function. Electrolytes and blood sugar should be monitored regularly and insulin infusion started if required to control blood sugar levels. Inotrope infusion may be required in haemodynamically unstable patients.[19] Antiarrhythmic drugs and defibrillators should be easily accessible. Arterial blood gas analysis should be carried out as indicated.[19]

*In-vitro* studies have shown isoflurane to have antifungal properties and its use is gaining interest in patients undergoing surgery for mucormycosis.[20] In healthy patients, intraoperative hypotension can be provided during FESS. Controlled hypotension is known to decrease intraoperative blood loss and improve surgical field visibility.[21,22] This can be done using dexmedetomidine infusion or other drugs.

Perioperative stress-dose steroid cover in these patients is debatable. Chronic steroid therapy can lead to secondary adrenal insufficiency which can manifest as adrenal crisis perioperatively. Inadequate cortisol production predisposes to vasodilatation and severe persistent hypotension unresponsive to fluids and vasopressors. Cortisol (100 mg) in normal saline is routinely used as the stress-dose steroid for major surgeries.[23] There are no clear guidelines indicating the dosage and duration of steroid therapy that can lead to secondary adrenal insufficiency. Prednisolone in a dose of 5 mg/day or its equivalent taken for more than 4 weeks has been reported to cause hypothalamic–pituitary–adrenal axis (HPAA) dysfunction.[24] The duration of recovery of HPAA suppression after discontinuation of steroids is also not clear. However, it is presumed that the suppression does not continue beyond 1 year after cessation of steroids.[23] Stress-dose steroids increase the risk of hyperglycaemia which needs rigid control in patients with mucormycosis.[23] Secondary adrenal insufficiency leads to glucocorticoid and not mineralocorticoid deficiency. The mineralocorticoid property of steroids can lead to dose-dependent fluid retention and hypokalaemia. Thus, if the dose of hydrocortisone exceeds 100 mg, it is advisable to use methylprednisolone which has a higher ratio of glucocorticoid-to-mineralocorticoid activity.[23]

Extubation at the end of surgery depends on various factors including the clinical status of the patient and the extent of surgery. Patients undergoing minimally-invasive procedures without airway-related complications can be extubated on the table. Patients on inotropic support or those who have undergone extensive surgery with excessive blood loss are often shifted to the ICU where they are gradually weaned off the ventilator. As airway oedema and trickling of blood from debrided areas can necessitate reintubation, patients should be monitored carefully in the postanaesthesia care unit following extubation.[19]

### *Postoperative management*

Good postoperative pain management can be provided by fentanyl infusion. Severe facial pain has been described after maxillectomy.[25] This type of pain is usually not relieved with analgesics and persists for many weeks after surgery. As this pain is usually due to reflex sympathetic dystrophy, Gasserian ganglion block or stellate ganglion block has been effective in relieving it.[25,26]

HBOT is used as an adjunct to debridement. HBOT helps in healing by revascularisation of viable but poorly perfused and hypoxic tissues.[27] At present, there is no evidence to prove that the use of industrial oxygen can predispose to a surge in mucormycosis. However, caution has been sounded against the use of contaminated oxygen delivery devices.[15]

## Summary

Successful outcome from ROCM depends on early diagnosis and emergent management. So far, uncontrolled diabetes has been delineated as a single major risk factor for mucormycosis making tight glycaemic control essential. Early surgical management is essential to stop mucor from spreading. Additional morbidities due to COVID-19 infection require thorough assessment and optimisation. Both mask ventilation and intubation can be difficult in these patients. Extubation at the end of surgery depends on the pulmonary status, haemodynamic stability and the extent of surgery. Anaesthetic management of these patients is often challenging as these patients have developed one

enfeebling disease after another. Meticulous preoperative evaluation and optimisation followed by a carefully planned anaesthetic often spells success.

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## Conflicts of interest

There are no conflicts of interest.

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