# Diagnosis and management of mucormycosis in the dental clinic: A guide for oral health professionals in India

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## **A**BSTRACT

With the current pandemic raging over the world, science and medicine is faced with hereto with unfought enemies or less fought opponent in the form of viruses and consequently, other biotic entities. While researchers are striving to identify and conquer the variants of COVID-19, other innocuous organisms are raising their ugly heads in the form of opportunistic fungal infections. Mucormycosis/Black Fungus is an invasive opportunistic fungal infection caused by *mucorale* species. It spreads through blood vessels causing thrombosis, ischemia, and necrosis. Population with pre-existing immunocompromised conditions such as Diabetes Mellitus, Malignancy, Long-term immunosuppressant therapy are more susceptible. Mucormycosis associated with Corona Virus Disease-2019 (COVID-19) proved to be catastrophic due to its high mortality rates. Rhino orbital Mucormycosis is the most common form. The primary care physician, being the first and often, (more so in developing countries) and being the only point of contact with a healthcare professional, plays a pivotal role in the diagnosis and management of this condition. The keystone to decreasing mortality is early detection and diagnosis followed by preventive measures to control progression to the brain. A multidisciplinary approach by various specialties is a prerequisite for effective diagnosis and management. Antifungal therapy, surgical debridement, and resection of the affected areas are protocols to be followed. Post-operative defects cause impairment of function, phonetics, and esthetics. Prosthetic rehabilitation of these defects has shown favorable results, especially in the aged and immunocompromised individuals.

Keywords: COVID-19, dentists, maxillary sinus, mucormycosis, opportunistic infections

#### Introduction

Coronavirus disease 2019 (COVID-19) has proved to be one of the most disastrous pandemics ever in the history of mankind, devouring a huge number of lives.

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Although several treatment protocols have been evaluated for its management, systemic glucocorticoids serve to be a life saver in many cases by improving the survival rates (2.8%) in COVID-19.<sup>[1]</sup> Systemic corticosteroids serve as a double-edged sword by giving favorable results and unfavorable consequences of producing immunosuppression leading to opportunistic infections.<sup>[2]</sup> The predominant fungal pathogens that cause co infection in COVID-19 patients are White fungus (Candida), Yellow Fungus (Aspergillosis), and Black Fungus (Mucormycosis).<sup>[3]</sup> The Yellow Fungus or

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Aspergillosis is an invasive fungal infection, the prevalence of which is documented to be 5-10 folds more common than Mucormycosis.<sup>[2]</sup> However, spike in the incidence of Mucormycosis is seen in COVID-19 affected individuals recently in India.[3] Mucormycosis is an aggressive, invasive, and potentially devastating opportunistic fungal infection first described by Paultauf in 1885.[2] It is crucial to pay attention to Mucormycosis among COVID-19 patients due to the increase in mortality rate (as high as 90%).[3] Globally, the prevalence of Mucormycosis varies from 0.005 to 1.7 per million population, whereas its prevalence is nearly 80 times higher (0.14 per 1000) in India as compared to developed countries, in a 2019-2020 estimate. [3] Oral Mucormycosis is usually caused by inhalation of spores or direct contamination of open oral wound.<sup>[4]</sup> Fungal spores by angioinvasion causes thrombosis leading to tissue necrosis, which is a classic feature of this disease. The family physician is often the first (and often the only healthcare provider) clinician to be approached for almost all ailments, thus placing the onus of either apt diagnosis or timely referral of this possibly lethal condition on their shoulders. The role of Oral Clinicians is of relevance as the condition primarily occurs around the rhinomaxillary or rhinocerebral areas involving facial tissues, palate, alveolar bone, and mandibular bone. Inhalation through nasal passage or infection of extraction sockets with sporangiospores in immunocompromised patients causes larger areas of necrosis along with systemic dissemination. [5] Treatment of deep fungal infections like Mucormycosis is arduous as the drug target sites of eukaryotic pathogens closely resembling those of the human host, which limits therapeutic options.[4]

Rhinocerebral mucormycosis variant, which is commonly associated with COVID-19, is a challenge to diagnose and manage. Early diagnosis is crucial, as a delay of 12 hours in diagnosis could turn out to be lethal for the patient.<sup>[3]</sup>

# The Black Fungus: Etiology and Predisposing Factors

Mucormycosis also known as Zygomycosis or Phycomycosis is as an insidious fungal infection caused by members of Mucorales and zygomycotic species. [6] It is frequently found in soil, residue of plants, spoiled food, and upper respiratory tract of healthy individuals.<sup>[7]</sup>

Rhizopus arrhizus (oryzae) is considered to be the most common organism associated with mucormycosis, which becomes pathogenic in susceptible individuals who are immunocompromised due to underlying diseases like Diabetes Mellitus, Malignancy, Renal failure, Liver diseases, Acquired immune deficiency syndrome, organ transplant patients under long-term immunosuppressant therapy, and other metabolic diseases. Among these, Mucormycosis was found to be more prevalent in patients with Diabetes Mellitus (60-81%).<sup>[7,8]</sup> Pathophysiology of this infection is presented in Figure 1.<sup>[9,10]</sup>

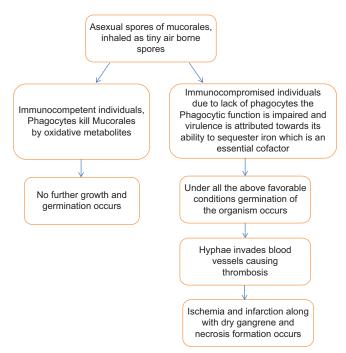


Figure 1: Pathophysiology of mucormycosis

# Clinical Features of Infection of the Oro-facial Region

Clinically Mucormycosis presents in various forms—Rhinocerebral, Gastrointestinal, Cutaneous, and Pulmonary depending on the site of ingestion/inoculation. Among these, the rhinocerebral form is considered to be most common involving the nasal and paranasal sinuses, extending to involve the orbits and the cranial system. It may be localized or disseminated based on the virulence and host defense mechanism.<sup>[4]</sup>

The Smith and Krichner (1950) criteria for the clinical diagnosis of mucormycosis are still considered to be the gold standard and include: (i) Black, necrotic turbinate's easily mistaken for dried, crusted blood, (ii) Blood-tinged nasal discharge and facial pain on the same side, (iii) Soft peri-orbital or peri-nasal swelling with discoloration and induration, (iv) Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia, and (v) Multiple cranial nerve palsies unrelated to documented lesions.<sup>[3]</sup>

Oral Mucormycosis occurs usually in association with the rhinocerebral form. Serious involvement of paranasal sinuses leads to palatal necrosis and/or ulceration leading to oroantral communication or perforation extending to facial tissues. [11,12] Clinical presentations are headache, fever, rhinorrhea, facial cellulitis, orbital, and neurological involvement. Recently, symptoms reported by COVID-19 patients who have acquired Mucormycosis are black or blood discharge from nose, facial numbness, and jaw pain with loosening of teeth mostly maxillary teeth, blackish discoloration of nasal bridge, and haziness in vision. [13]

## **Predisposing Factors in COVID-19**

Pulmonary mucormycosis typically develops in patients with profound neutropenia and graft-versus-host disease, whereas diabetic patients typically present with rhino-orbital disease. [14] Singh *et al.* conducted a systematic review that reported the findings of 101 confirmed mucormycosis cases in individuals with COVID-19; Diabetes Mellitus was reported in 80% of the cases, whereas 76.3% were receiving corticosteroids. Diabetic ketoacidosis is often observed due to corticosteroid intake. The acidic environment is a fertile media for mucor spores to germinate. Endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in CD4+ and CD8+ level are other effects of COVID-19 affected individuals that predisposes to mucormycosis. [3]

## **Investigations**

Although mucormycosis presents with necrosis and specific signs and symptoms, clinically they mimic various other diseases. Hence, it is essential to run the gamut of investigations to arrive at a confirmatory diagnosis [Table 1].

## **Staging of Mucormycosis**

Staging is important to read the extent of invasion for precise treatment and management of the infection.

Based on the areas of involvement, Rhino Orbital cerebral Mucormycosis staging is as follows:

**Stage 1:** Involvement of nasal mucosa **1a:** Limited to middle turbinate **1b:** Involvement of inferior turbinate **1c:** Involvement of nasal septum.

**Stage 2:** Involvement of paranasal sinuses **2a:** One sinus **2b:** Two ipsilateral sinuses **2c:** Two ipsilateral sinuses and or palatal or oral cavity **2d:** Bilateral paranasal sinuses/zygoma/mandible.

Stage 3: Involvement of orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement, vision unaffected 3c: Central retinal artery/ophthalmic artery occlusion or superior ophthalmic vein thrombosis, involvement of superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement.

**Stage 4:** Involvement of CNS **4a:** Focal or partial cavernous involvement and or involvement of cribriform plate **4b:** Diffuse cavernous sinus involvement/cavernous sinus thrombosis **4c:** 4b plus involvement of skull base, internal carotid occlusion, brain infarction **4d:** Multifocal/diffuse CNS disease. [13]

Table 1: Investigations techniques for the diagnosis of Mucormycosis		
Investigations	Diagnostic features	
Imaging Techniques		
Radiograph	Opacification is seen in case of mucormycosis Aspergillosis shows radiological concretions in radiograph. [15]	
Computed Tomography (CT) Lungs	Mucormycosis shows reverse halo sign (RHS) - an area of ground glass opacity surrounded by a ring of consolidation on thoracic CT, or vessel occlusion on CT pulmonary angiography[9,14]	
CT Cranial	Involvement of sinuses and extent of bone destruction can be examined, <sup>[14]</sup> Foci of hyperdensity in the affected sinus on CT scans are highly suggestive of fungal disease. CT is 100% sensitive and 78% specific in the diagnosis of sinonasal mycosis, <sup>[15]</sup>	
Magnetic Resonance Imaging (MRI) Cranial	Involvement of Brain and orbit <sup>[14]</sup>	
Cone Beam Computed	In CBCT the mucormycosis is depicted as erosion due to osteolysis of bone, perforation of palate to the	
Tomography (CBCT) [Figure 2]	maxillary sinus and extent of mushrooming of the infection can be seen in three-dimensional view. <sup>[16,17]</sup>	
Laboratory Techniques		
Culture and Microscopy	Mucorales in potato dextrose agar and Saboraud grown upto 3–7 days when incubated at 25°. [9] Impression: Cottony white or grayish black colony. [14]	
Serology	Galactomannan, 1,3-β-D-glucan is Positive for mucormycosis	
	ELISA assays immunoblots and immunodiffusion tests are invasive towards Mucorales and mucormycosis. <sup>[9]</sup>	
Biopsy		
Direct Microscopy	Stained with fluorescent brighteners calcofluor white or blankophor. [14]	
Histopathology	Hematoxylin-eosin (HE), periodic acid-Schiff stain (PAS) or Grocott-Gomori's methenamine-silver staining shows broad, non-septate type of hyphae with the pathognomonic nature of hyphae branching at right angles. [9,14] The 90° branching angle of Mucorales in tissue versus 45° branching angle of septate moulds aspergillus can be difficult to differentiate due to interstitial pressures exerted on the fungi by the tissue during processing. Thus the wider and irregular (ribbon-like) nature of the hyphae are more reliable distinguishing characteristics than septations and angle of branching. Acute lesions: Hemorrhagic infarction, coagulation necrosis, angioinvasion, infiltration by neutrophils and perineural invasion are characteristic features.	
	Chronic lesions: Presence of giant cells, and deeply eosinophilic material surrounding the pathogen is seen (Splendore-Hoeppli phenomenon) <sup>[14]</sup>	
Molecular staining	Immuohistochemical staining using specific antibodies to distinguish between Mucorales and Aspergillus. Polymerase Chain reaction on either fresh or formalin-fixed paraffin-embedded tissue shown to be highly specific, although a variation in sensitivity has been reported. <sup>[14]</sup>	

Table 2: Comprehensive management of the infection		
Specialty	Role in management	
Role of Oral Physician and Radiologist	Administration of systemic antifungal medication is the first line of treatment. Amphotericin-deoxycholates and lipid complex which are polyenes are primary therapeutic agents for mucormycosis, however it is pertinent to monitor electrolyte levels as polyenes causes imbalance in potassium levels. Posaconazole, which is structurally similar to itraconazole, has generally been considered the second-line or salvage therapy for patients intolerant to amphotericin B. [10]	
Role of Oral and Maxillofacial Surgeon	Although antifungal medications are administered, surgical debridement necessary in many cases to prevent further progression. [7,18,19] Functional endoscopic sinus surgery (FESS) under general anesthesia for sequestrectomy of maxilla, total curettage, and complete debridement of the maxillary antrum are the surgical procedures performed by Oral and Maxillofacial Surgeons. [4,23] Recently, Hyperbaric oxygen therapy is employed that suppresses fungal growth by reducing tissue hypoxia and acidosis, which are ideal growth factors for the fungus and also have found to increase the survival rate by 94% [7,18]	
Role of Periodontist	Role of Periodontist in diagnosis and management of mucormycosis is significant as most of the systemic and immunocompromised conditions are reflected in the gingiva of the oral cavity. Diabetes Mellitus, Leukemia, drug induced gingival hyperplasia dues to immunosuppressants are all reflected in the periodontium. McDermott <i>et al.</i> <sup>[24]</sup> have reported a case on periodontal mucormycosis in a leukemic patient, which was diagnosed and treated appropriately thereby preventing its spread to the palate and adjacent structures.	
Role of Prosthodontist	Surgical resection despite being a life-saving procedure can cause huge defects over the affected areas, and hamper the individuals' lifestyle due to cosmetic and functional concerns.  Surgical reconstruction is necessary to rehabilitate the defects; however Prosthetic rehabilitation is widely practiced due to various advantages. The inherent advantages of Prosthetic rehabilitation are that it is an ideal treatment for aged and medically compromised patients, which avoids multiple surgeries, noninvasive, easy to cover larger defects and with predictable outcomes. [25]  Maxillary defects without orbital involvement is rehabilitated with Hollow Bulb Obturator. Complex facial defects involving the orbit are corrected using the hollow bulb obturator with orbit. Retention of the obturator involving the orbit is gained using a spectacle (eyeglass) frame, extensions from the obturator, magnets and buttons, engaging tissue undercuts, adhesives or osseointegrated implants. [25] At times, using magnets and buttons may cause movement of the prosthesis if there are multiple maxillary defects and in such cases, brass cylinders and housing are used to restore the defect.  In case of dentulous patients, the surgeon focuses on saving as many teeth as possible for the purpose of retention of the prosthesis. [25]  Complete submaxillectomy is done in cases involving bilateral maxilla and sinus. In these cases, the patient becomes completely edentulous with an open communication between the oral and the nasal cavity thereby affecting function, phonetics, and esthetics. Operative, Pre-operative, and post-operative prosthesis are fabricated in these cases. A surgical obturator is fabricated to be used during surgery, an interim obturator is fabricated and utilized during the wound healing phase and finally a definitive obturator is	

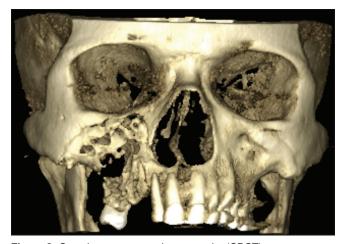


Figure 2: Cone beam computed tomography (CBCT)

## **Role of Dentists in Prevention**

Sterilization is an imperative procedure to be followed in hospitals and clinical setups as the spores are found in contaminated air, water, and surfaces in hospitals. A study has observed that among 75 cases of mucormycosis in India, about 9% of the cases were due to nosocomial infection. Usage of non-sterile products, contaminated tongue depressant and instruments in the oral cavity, procedures like tooth extraction and surgeries using unsterile materials can make an immunocompromised patient more vulnerable to the disease. [13] Hence, a sterile clinical or hospital setup is mandatory.

# Role of Dentists in the Management of Mucormycosis

Dentists play a crucial role as most COVID -19 associated mucormycosis primarily occurs around the rhinomaxillary or rhinocerebral areas involving facial tissues, palate, and alveolar bone.<sup>[5]</sup> In particular, oral symptoms become evident at the initial stage of the infection, hence prompt diagnosis is crucial. As mentioned earlier, undiagnosed cases can progress to fatal effects such as spreading to the brain and associated structures due to its angio-invasive property. [18] Survival rates among groups of patients with invasive sinus disease without cerebral involvement may be as high as 50–80%; if infection spreads to the brain, case fatality ratios exceed 80%. [15] Four factors are critical in managing mucormycosis: rapidity of diagnosis, reversal of the underlying predisposing factors (if possible), appropriate surgical debridement of the infected tissue, and appropriate antifungal therapy. [15] Following diagnosis, a multidisciplinary approach is required to restore the structure, function, and esthetics of the individual.

# Early Diagnosis: A Critical factor in managing Mucormycosis

Before proceeding with clinical examination, a comprehensive history of the patient is required. Recent history of COVID-19 hospitalization and treatment for the same is another vital pointer in history owing to the existing pandemic. However, a few case

reports have proved that immunocompetent patients have also acquired Mucormycosis. Soni *et al.*<sup>[18]</sup> have reported a case of paranasal mucormycosis in an immunocompetent individual, where the patient revealed a brief history of Chronic Sinusitis. This individual become susceptible to Mucormycosis due to mucociliary dysfunction and alteration in immune defence. Gupta *et al.*<sup>[19]</sup> have reported a case of an immunocompetent individual who suffered from Mucormycosis due to dental manipulation and emphasized the importance of recording the history of patients who report with signs and symptoms of the condition.

There also exists reports of cases that posed a diagnostic dilemma. Rai *et al.*<sup>[20]</sup> reported a case of maxillary mucormycosis, which was masquerading as osteomyelitis. Pereiro-Filho *et al.*<sup>[21]</sup> have reported a case of mucormycosis, which was mistaken for maxillary sinusitis and has discussed the importance of investigations pertinent to arrive at a final diagnosis. Possible differential diagnosis for oral mucormycosis include tertiary syphilis, Wegener's granulomatosis, carcinoma of the palate (squamous cell carcinoma/mucoepidermoid carcinoma), midline lethal granuloma, osteomyelitis, tuberculosis, other deep fungal infections, and ulcer due to bisphosphonate therapy.<sup>[22]</sup>

# Comprehensive Management of the Infection [Table 2]

#### **Conclusions**

Mucormycosis is a fulminating disease with immense potential for rapid spread. A multidisciplinary approach by a team of clinicians with emphasis on recording a detailed history, clinical examination, early detection and diagnosis, preventive antifungal medication, surgical management, prosthetic rehabilitation, and correction of surgical defect has proved to decrease the mortality rate and improve the quality of life of individuals. Published research on posaconazole (injectable), a triazole, antifungal agent that considerably eases the pressure and offers patients much needed and timely therapy options and simple procedures such as saline nasal irrigations must be borne in mind while managing this condition. [27,28] The primary care physician/healthcare worker is duty bound to evolve and upgrade their expertise in order to productively contribute towards the preservation and welfare of mankind when faced with adversities such as this pandemic and play their role as healthcare providers in society.

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### **Conflicts of interest**

There are no conflicts of interest.

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