



**A FATAL FUNGI: MUCORMYCOSIS IN CHILDREN, A CONCERN TO PEDIATRIC DENTIST**

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**ABSTRACT**

**Objectives:** To determine the various clinical effects of Mucormycosis and its management in children and the association of mucormycosis with Covid 19 pandemic. **Data and Sources:** A search for the published literature was done through the National library of medicine (PubMed) and Google Scholar using the search terms: Mucormycosis, Zygomycosis, Mucorales, and Fungal infection in children. **Study selection:** Studies with the clinical manifestations of mucormycosis, epidemiology of mucormycosis, the various diagnostic aids available, the prevention and further management after its onset in children were included in this review. **Conclusions:** This review gives a brief idea regarding the forms of mucormycosis, of which the invasive mucormycosis is fatal which is of concern to dentist. Hence by controlling the etiological risk factors, mucormycosis can be prevented. **Clinical significance:** As mucormycosis has become one of the life threatening emergencies, mainly in the Covid 19 pandemic, the prevention and management of various types of mucormycosis in both children and adult could be possible by using the various diagnostic aids which helps to delineate this mucormycosis from other fungal infections.

**KEYWORDS:** Mucormycosis, Mucorales, Children, Covid 19 associated Mucormycosis, Pediatric Dentistry, and Types of Mucormycosis.

**INTRODUCTION**

The progressively arising trend of diseases caused by the fungal organisms in human population have given a great challenge to the healthcare professionals.<sup>[1]</sup> There are approximately 400,000 fungal species of which 400 are human pathogens. Fungi are the organisms which is found everywhere hence called as ubiquitous,<sup>[2]</sup> of which medically important were of two types: Primary and Opportunistic. Primary infections of fungal origin are seen most commonly in individuals who are healthy enough while opportunistic infections are seen in individuals who have low immune responses. The other common types includes invasive and non-invasive fungal infections. Invasive forms were caused mostly because of the existence of yeast and were considered fatal as they attack various organs such as brain. In humans the commonly found fungal infection are Candidemia, followed by Aspergillosis and then Mucormycosis.<sup>[1]</sup>

In the last decade mucormycosis was seen affecting both adults and children in individuals who have associated blood malignancies, increased blood glucose level (diabetes mellitus), patients who had trauma and those undergoing treatment with deferoxamine. Children with type 1 diabetes mellitus (juvenile-onset), uncontrolled

diabetic ketoacidosis, and congenital metabolic aciduria are more prone to develop mucormycosis. Treatment of mucormycosis with certain antifungals and surgery have significantly improved the outcome and prognosis of the fungal disease.<sup>[3]</sup>

**Define mucormycosis?**

Mucormycosis is an infectious condition caused by a bunch of fungal moulds called Mucormycetes. It is mis-judged as Black fungus because the infectious disease induced by the fungal organism mucorales in host causes black pigmentation. Dematiaceous fungi commonly known as black fungi produces black yeasts.

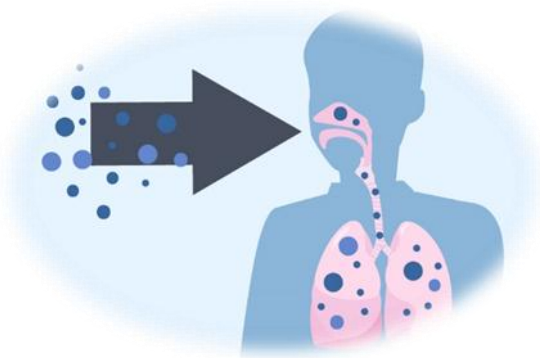
**Microbiology of mucormycosis**

Mucormycosis which was previously known as Zygomycosis belongs to a class of fungus called Zygomycetes which contains mucorales. Mucorales causes mucormycosis, a deadly fatal and an invasive form of fungal infection which mostly affects the immunocompromised patients.<sup>[4]</sup>

Mucorales consists of 6 families which include.

Family	Genus	Species	
Mucoraceae	Absidia	A. corymbiferadi	
	Apophysomyces	A. elegans	
	Rhizopus	R. pusillus	
		R. arrhizus	
		R. azygosporus	
	Mucor	M. circinelloides	
		M. hiemalis	
		M. racemosus	
		M. ramosissimus	
	Cunninghamella	C. bertholletiae	
Mortierella	Mortierella		
Saksenaea	Saksenaea	S. vasiformis	
Syncephalastrum	Syncephalastrum	S. racemosum	
Cokeromyces	C. recurvatus		

The most common cause of mucormycosis was due to Mucoraceae, of which the most common species causing it was *Rhizopus arrhizus* (oryzae) followed by *Rhizopus microsporus* var. *microsporus*, *Rhizopus* *microsporus* var. *microsporus*, *Rhizopus* *microsporus* var. *microsporus*, *Cunninghamella bertholletiae*, *Apophysomyces elegans*, and *Saksenaea vasiformis*.<sup>[4]</sup> Mucorales which cause mucormycosis are considered as ubiquitous and they commonly grows on dead and decaying organic material. The mucorales invades the deeper tissues in humans, through airborne, gets inoculated percutaneously or by ingestion. The most common site of invasion of mucorales are sinuses which accounts for approximately 39%, followed by lungs - 24%, skin (epidermis) - 19%, brain - 9%, gastrointestinal tract -7% and lastly disseminated disease - 6%.<sup>[5]</sup>



### History, Epidemiology and Prevalence

Mucoralean fungi can cause infection in both human and animals.<sup>[6]</sup> The mucormycosis cases reported with mucorales were seen to increasing rapidly, this might be due to the increased awareness and development of newer molecular diagnosis methods.<sup>[7]</sup>

The highest prevalence of mucormycosis according to Jeong et al. (2019) was seen in Europe (34%), followed by Asia (31%) and the lowest was seen in Australia and New Zealand (3%).<sup>[8]</sup> Chakrabarti A et al (2019) reported

that of the mucormycosis cases, 24 % of all infections were caused by invasive mould infections.<sup>[9]</sup>

The epidemiological studies stating the occurrence of mucormycosis in children are rare and about 50 % of the cases were seen in relation to hematological malignancy and cancer.<sup>[10]</sup> Among the Asian continents, the highest occurrence of mucormycosis infection was seen in Asian countries like India and China in patients with uncontrolled hyperglycemic condition (diabetes mellitus).<sup>[11]</sup>

### RISK FACTORS

**Adults:** Petrikos G et al in 2012 reported that any dysfunctioning in the immune function could be one of the factor. According to Francis et al (2018) the other risk factors include hematologic malignancy, diabetes (9 % to 36 %), excess iron in the body, patients under the medication deferoxamine, individual who use drugs intravenously, and renal failure (found mostly in adults), burns and traumatic wounds, underlying rheumatologic/autoimmune disorders.<sup>[12]</sup>

**In children:** The risk factors includes neutropenia – decreased in neutrophil count (18%), any associated malignancy (16%), in case of bone marrow transplantation (6%), hyperglycemic conditions (15%) and ketoacidosis (10%). Prematurity as a co-morbid condition was also seen in children (17%) with Zygomycosis and about 14% proportion of patients reported had no apparent immunocompromising condition. The independent risk factors seen in children were found to be disseminated infection and young age. The mucormycosis which commonly occurs in neonates were found to be gastrointestinal (51.0%) as well as cutaneous (35.6%) disease. A high mortality rate of about 78 % was seen in children with gastrointestinal mucormycosis, as they often go undiagnosed. The cutaneous type of mucormycosis, which commonly occurs in neonates were caused mainly due to the

unsterile use of wooden tongue depressors or venipuncture's.<sup>[13]</sup>

### Diabetes Mellitus and Ketoacidosis

Diabetes is considered as one of the most common underlying etiological cause for the occurrence mucormycosis.<sup>[14]</sup> According to the WHO's global report on diabetes in 2016, it was seen that there was an increase in the incidence and prevalence off diabetes from 4.7% to 8.5% and the rise was seen higher and faster in low and middle income countries.<sup>[15]</sup> According to Prakash H et al in 2019, in India it was seen that about 73.5 % of cases of mucormycosis was due to Diabetes. It was also reported that 90 % in North India and 10 % in South India was due to Ketoacidosis<sup>[16]</sup> Increased mortality rate of mucormycosis associated with Diabetes mellitus was seen in young children.<sup>[17]</sup>

### Hematological Malignancy and Hematopoietic Stem Cell Transplantation

The cancer that affect the blood, bone marrow and lymph nodes are called as hematological malignancy.<sup>[18]</sup> The most commonly seen hematological malignancies are acute myeloid leukemia(AML), acute lymphoid leukemia (ALL), lymphoma, hairy cell leukemia and Hodgkin's disease<sup>[19]</sup> In children the highest chance of developing mucormycosis was seen in relation to a condition called neutropenia.<sup>[20]</sup> Patel et al (2020) reported that an incidence of about 1 % cases in India.<sup>[21]</sup>

### Organ Malignancies and associated organ transplantation

According to Alymyroudīs et al (2006) the highest prevalence was seen in patients undergoing lung transparent (13.7 – 14 %) followed by heart transplant (8 %), liver transplant (4-16 %) and renal transplant (0.4 – 0.5 %).<sup>[22]</sup>

### Corticosteroids, Immunosuppressive agents and autoimmune diseases

According to Kontoyiannis et al (2011) prolonged use of systemic high dose of corticosteroids for more than 3 weeks was found to a main risk factor causing mucormycosis.<sup>[23]</sup> Hoang et al (2020) reported that short courses of corticosteroids could also be a risk factor.<sup>[24]</sup> The global prevalence of mucormycosis due to autoimmune disease was found to be around 3 % (Jeong et al, 2019).<sup>[8]</sup>

### Increase Iron load in serum

Increased iron is also found to be a risk factor of mucormycosis and was found in relation to diabetic ketoacidosis, patients undergoing dialysis, multiple blood transfusions.<sup>[25]</sup>

### Others

In a study by Prakash et al (2019) it was seen that 6.9 % of post pulmonary tuberculosis and 8.9% of patients with chronic kidney disease were considered as possible risk factors<sup>[16]</sup> Mucormycosis has also been reported in

association with trauma and combat related injuries in children.<sup>[26]</sup>

### Health care associated mucormycosis

Healthcare associated mucormycosis was seen mostly due to following reasons.

- Unsterile products – bandages, adhesives, nitroglycerin patches.
- Environmental factors.
- Instrument used in various procedures such as catheters, insulin pumps and finger sticks<sup>(27)</sup>

From the above underlying conditions it was shown that source of infection and the risk factors associated determines the prognosis.

### Types

Based on the anatomical site,

- ROCM, rhino-orbital-cerebral mucormycosis, the commonest form (45–74%)
  - Cutaneous mucormycosis (10–31%),
  - Pulmonary mucormycosis (3–22%),
  - Renal mucormycosis (0.5–9%),
  - Gastrointestinal mucormycosis (2–8%),
  - Disseminated infection mucormycosis (0.5–9%),
- In India the other unusual sites of development of mucormycosis includes: breast, ear, spine, heart , and bone infections.<sup>[28]</sup>

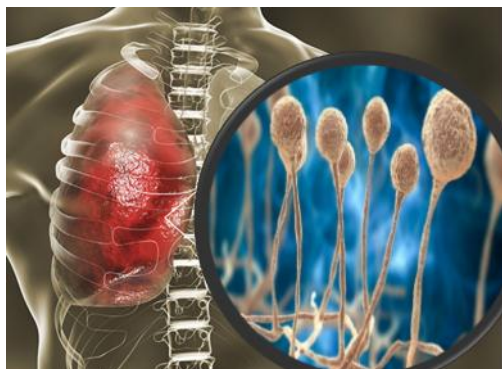
### Clinical Manifestations

**ROCM, rhino-orbital-cerebral mucormycosis:** Patel et al (2020) reported that 77 % of ROCM was due to diabetes<sup>[21]</sup>, while 15-52 % were due to trauma associated with unhygienic procedure during tooth extraction.<sup>[16]</sup>



**ROCM, rhino-orbital-cerebral mucormycosis**

**Pulmonary mucormycosis:** Solid organ transplant (SOT) (37–44%), malignancies related to blood (10–26%), and diabetes mellitus (10–14%) are some of the predisposing factors which causes pulmonary mucormycosis.<sup>[8]</sup> According to Prakash H et al (2019) post pulmonary tuberculosis (38%) was found to be a new underlying condition for the occurrence of pulmonary mucormycosis.<sup>[16]</sup>



**Cutaneous mucormycosis:** 45–79% of cutaneous mucormycosis was seen in relation with trauma in India.<sup>[29]</sup> Kaushik et al (2012) in his study on Indian population analyzed that cutaneous mucormycosis was seen in higher association with trauma (59 %) which was then followed by diabetes mellitus (28%) and Cancer (6%).<sup>[30]</sup>



**Gastrointestinal mucormycosis:** Kaur H et al (2018) in his study on Indian population, found that 2- 8% of gastrointestinal cases found where seen in association with 60 % of pediatric populations, with 83 % in premature neonates.<sup>[31]</sup> Patel et al (2020) reported that around 25- 50% of gastrointestinal mucormycosis reported in India was mainly due to the diabetes mellitus.<sup>[21]</sup> Patra et al (2012) found that 20% of gastrointestinal mucormycosis was seen in neonates with necrotizing spondylitis with 83 % of them were preterm neonates.<sup>[32]</sup>

**Renal mucormycosis:** Seen most commonly in immunocompetent patients.<sup>[29]</sup> Renal involvement of mucormycosis is extremely rare. This can be of two types: disseminated renal mucormycosis and primary renal mucormycosis in children.

The common symptoms in patients with mucormycosis includes headache, chemosis, multiple paresis of the cranial nerve, unilateral facial pain around the orbital region, proptosis (bulging of the eye), blepharoptosis (drooping or falling of the upper eyelid), changes of

ocular motility, ophthalmoplegia (paralysis of the motor nerves of the eye) and loss of eyesight (vision).<sup>[33]</sup>

### Oral Manifestations

The oral manifestation of the fungal infection could be due to the close association of the oral cavity with the nasal cavity.<sup>[34]</sup> The rhinocerebral mucormycosis appears in two forms: highly fatal form and less fatal form. The highly fatal form affects the ophthalmic (a part of internal carotid artery), while the less fatal form affects the sphenopalatine and greater palatine arteries (parts of maxillary artery), which ultimately causes thrombosis & necrosis of the turbinate & palate of the maxillary bone. The palate undergoes ischemic necrosis of the mucoperiosteum followed by bone denudation. Ulcers due to mucormycosis were reported on gingiva, lips, alveolar ridge, cheek, tongue as well as on the mandible.<sup>[33]</sup>



Ulcer - alveolar bone of left lateral incisor and canine<sup>[35]</sup>

### Covid 19 and its association with mucormycosis

Covid 19, a contagious and an infectious disease which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>[36]</sup> Fungal infection like mucormycosis has been seen associated with covid 19 which have resulted into various fatal consequences. Critically ill covid 19 pediatric patients who required systemic steroid, admitted to intensive care unit and who require mechanical ventilation for a prolonged period of time were likely to develop mucormycosis infection.<sup>[37]</sup> In a report by American Society of microbiology, covid 19 associated with mucormycosis was considered as a “Triple threat of the Pandemic”.<sup>[38]</sup>

### Diagnosis

Early diagnosis prevents various complications.<sup>[39]</sup> Diagnosis can be of two type clinical diagnosis, routine laboratory diagnosis, applied and emerging molecular methods and non-invasive methods.

### Clinical Diagnosis

The distinctive characteristic feature associated with mucormycosis is that tissue necrosis which occurs as a result of angioinvasion and thrombosis.<sup>[40]</sup>

Warning signs or red flags, for the rhino-orbital –cerebral form of mucormycosis was reported by Corzo- Leon et al



(2018) and these signs includes cranial nerve paresis, double vision, pain in the sinus region, bulging of the eye, swelling around the orbital region, orbital apex syndrome and a ulcer in the palate.<sup>[41]</sup>

### Laboratory Diagnosis

Diagnosis of the type of fungal infection could be done by histopathological methods. Hematoxylin and eosin stain which is routinely used shows only the cell wall of the fungal species. The stains which specifically highlights the fungal species are grocott methenamine - silver and periodic acid schiff (PAS) stain.<sup>[42]</sup>

#### 1. Direct Microscopy

A rapid presumptive diagnosis can be done by direct microscopy with KOH, to determine the species or genus of the fungal species by its characteristic features.<sup>[43]</sup>

#### 2. Culture

Mucorales are thermo-tolerant i.e., they grow rapidly grow at a temperature of 37°C.<sup>[40]</sup> Mucorales could be cultured on matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF)<sup>[44]</sup> Positive culture, confirms the diagnosis of mucormycosis if the sample is taken from sterile site and positive culture could be contaminant if the sample is taken from non-sterile site.<sup>[43]</sup>

### Non-invasive Diagnostic Methods

#### 1) Molecular

Highly reliable tool for the diagnosis of invasive mucormycosis in immunocompromised patients was found to be serum mucorales polymerase chain reaction. qPCR are highly sensitive and its sensitivity in blood is lower than that in tissues.<sup>[45]</sup>

#### 2) Serology

Burnham et al (2018) found that a monoclonal antibody (2DA6) in a sandwich ELISA as a highly reactive tests for the detection of mucorale species.<sup>[46]</sup>

#### 3) Metabolomics Breath Test

Koshy et al (2017) found that the fungal species produces distinct breath profiles of the volatile metabolite sesquiterpene. Thus, this could be used to identify the infections non-invasively.<sup>[47]</sup>

### Prevention of mucormycosis

ICMR (Indian Council of Medical Research) stated that mucormycosis mainly affects people who are on medication that reduces their ability to fight environmental pathogens.

- Control and monitor high blood glucose level especially in post COVID-19 patients.
- Steroid, antibiotics and antifungals should be used according to physicians advice following the correct timing, correct dose and duration.
- Clean and sterile water should be used for humidification of oxygen therapy.

- Never miss warning signs and symptoms of mucormycosis (red flag sign's).
- Never hesitate to seek investigations like KOH staining & microscopy, culture, MALDITOF, for detecting the presence of fungal infection and never delay to seek treatment for mucormycosis.<sup>[48]</sup>

### Management

Invasive mucormycosis could be managed by surgical debridement or antifungal therapy or combination of both.<sup>(2)</sup> In a study by Pana ZD et al (2016) it was found that a case fatality rate of 18.5 % in patients who underwent Surgery when compared with the case fatality rate of 60 % in patients who underwent antifungal therapy.<sup>[49]</sup> Surgical debridement could be used for the management of cutaneous mucormycosis. Antifungal drugs like amphotericin B (AmB), Isavuconazole (a novel triazole – wide spectrum) have activity against mucorales.<sup>[12]</sup> First line of antifungal therapy: Liposomal amphotericin B drug in a dosage of 5 – 10 mg/kg bodyweight could be prescribed, if renal toxicity arises then the dosage can be reduced to about 5 mg/kg. Amphotericin B lipid complex 5 mg/kg and Isavuconazole in case of moderate strength mucormycosis. If mucormycosis with CNS involvement is seen then a dosage of 10 mg/kg body weight could be used.<sup>[43]</sup> However the total duration of the antifungal therapy varies based on the patient's characteristics, extent, type and prognosis of the infection.<sup>[50]</sup>

### SUMMARY AND CONCLUSION

The invasive form of mucormycosis has a high case fatality rate of 47 % to 56 % and it had risen upto 96 %.<sup>[7]</sup> Hospital acquired and Covid 19 associated mucormycosis has been emerging nowadays. Patients with diabetes, immunocompromised conditions, under steroid therapy are prone to develop mucormycosis. Diagnosis plays an important part in the management of the fungal infection.<sup>[39]</sup> The surgical management of invasive form of mucormycosis should be considered in order to prevent the contagious spread of this infections to other sites. Antifungal therapy should also be considered until there is clinical resolution of the signs and symptoms associated with mucormycosis.<sup>[12]</sup>

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