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## Misfortune Never Comes Alone - The New “Black Fungus” Accompanying COVID-19 Wave

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### Abstract

**M**ucormycosis is a rare angio-invasive illness caused by the fungi Mucorales, which is often seen in immunocompromised patients. Rhino-orbitocerebral, cutaneous, disseminated, gastrointestinal, and pulmonary forms of this unusual fungal infection exist. Dr. Akshay Nair, a Mumbai-based eye surgeon, was waiting to operate on a 25-year-old woman who had recovered from Covid-19 three weeks prior on 8<sup>th</sup> May 2021 morning. He inserted a tube into her nose and was scraping mucormycosis-infected tissues, an uncommon but harmful fungal infection. The nose, eye, and even the brain are all affected by this violent infection. Doctors are now registering a number of cases involving a mysterious infection - also known as the “black fungus” among returning and recovered Covid-19 patients as a deadly second wave of Covid-19 ravages India.

### Introduction

**M**ucorales and Entomophthorales are the two orders that make up the Zygomycetes class. The infections produced by these two orders are vastly different. Mucormycosis is an angioinvasive infection caused by Mucorales genera (Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Cunninghamella, and Saksenaia). Mucormycosis may affect the rhino-orbitocerebral area, the lungs, the skin, or the gastrointestinal tract. Immunosuppressive conditions including haematological malignancies, bone marrow or peripheral blood stem cell transplantation, neutropenia, strong organ transplantation, diabetes mellitus with or without ketoacidosis, corticosteroids, and deferoxamine treatment for iron overload make patients more susceptible to infection. Mucormycosis is uncommon in immunocompetent hosts and is often linked to trauma. Depending on the patient’s underlying disease and type of mucormycosis, mortality rates can reach 100%. A good outcome requires early diagnosis, treatment of the underlying medical condition, surgery, and the use of an amphotericin B product.

In immunocompetent patients, the entomophthorales cause entomophthoromycosis, a chronic subcutaneous infection. Tropical and subtropical conditions are conducive to the spread of this infection. Basidiobolus is a genus of bacteria that causes a chronic subcutaneous infection of the hip, buttock, and/or trunk. It has been documented to affect the gastrointestinal tract on rare occasions. A chronic infection of the nasal submucosa and subcutaneous tissue of the nose and face is caused by the genus Conidiobolus. Mucormycosis was first reported in 1885, when German pathologist Paltauf identified the first case as Mycosis Mucorina (Mohammadi *et al.*, 2014). Mucormycosis agents must scavenge ample iron

from the host for growth, evade host phagocytic defence mechanisms, and gain access to the vasculature to disseminate in order to cause disease. Primary defence mechanisms against mucormycosis in a normal host include sequestration of iron in serum by specialised iron-binding proteins, phagocytes including circulating neutrophils and tissue macrophages, and endothelial cells that control vascular tone and permeability (Figure 1). These processes, when working together, avoid infection in tissue and eventual endovascular invasion. Standard defence mechanisms in susceptible hosts are disrupted (Spellberg *et al.*, 2005).

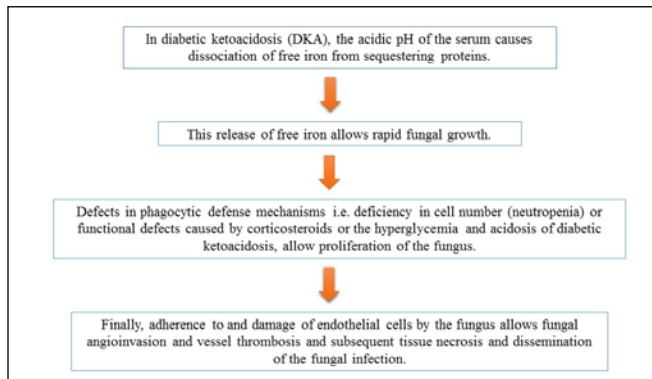


Figure 1: Pathogenetic mechanisms of and host defense mechanisms against mucormycosis

In the 1980's and 1990's, the rate of mucormycosis increased rapidly, mostly among immunocompromised people (Roden *et al.*, 2005). Mucor mould, which is commonly found in dirt, seeds, manure, and rotting fruits and vegetables, causes mucormycosis. It affects the sinuses, the brain, and the lungs, and it can be fatal in diabetics or people who are seriously immunocompromised, such as cancer patients or HIV/AIDS patients. Doctors conclude that the use of steroids, a life-saving therapy for serious and critically ill Covid-19 patients, could be triggering mucormycosis, which has a 50% overall mortality rate. Steroids tend to prevent some of the damage that can occur when the body's immune system goes into overdrive to combat the coronavirus by reducing inflammation in the lungs. However, in both diabetic and non-diabetic Covid-19 patients, they lower immunity and raise blood sugar levels. It is thought that this drop in immunity could be triggering these cases of mucormycosis.

## The Case Studies of Mucormycosis in India

It is a dangerous infection, despite its rarity. It is caused by a group of moulds known as mucormycetes, which are found in nature. According to experts from the Covid-19 task force, it mostly affects people who are taking medicine for health conditions that inhibits their ability to combat environmental pathogens. After inhaling fungal spores from

the air, these people's sinuses and lungs become infected. Mucormycetes may not usually pose a significant threat to people who have a strong immune system. Fever, headache, coughing, shortness of breath, bloody vomits, and altered mental state are all warning signs, as are pain and redness around the eyes or nose.

Sinusitis, nasal blockage 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, loosening of teeth, jaw involvement, blurred or double vision with pain, thrombosis, necrosis, skin lesion, thrombosis, necrosis, skin lesion, thrombosis, necrosis, skin lesion. Although the number of cases is increasing, there has been no significant outbreak. At a press conference, NITI Aayog Member (Health) Dr. V K Paul said there had been no major outbreak and that they were monitoring cases registered. Mucormycosis cases are on the rise in Maharashtra, according to Dr. Tatyrao Lahane, head of the Directorate of Medical Education and Research. In January this year, Dr. Rajeev Soman, an infectious diseases consultant in Pune, wrote in the Journal of the Association of Physicians of India that Mucormycosis emerging in a post-Covid-19 setting breaks the back of a patient's family that is barely recovering from this viral infection. Patients most vulnerable to mucormycosis are those who have been treated with steroids and other drugs for Covid 19 to reduce inflammation.

According to a report of India Today on May 12, 2021, Thane district in Maharashtra reported 2 more deaths caused by the black fungus. Moreover, six other patients in Thane are undergoing treatment for the black fungus infection. Maharashtra health minister Rajesh Tope has said the state could have as many as 2,000 cases of mucormycosis or black fungus. The state government has decided to use hospitals attached to medical colleges as treatment centres for mucormycosis. Jaipur has seen 14 patients with black fungus infection. Two from Ranchi, four from Rajasthan, five from Uttar Pradesh and the rest from Delhi-NCR have reached Jaipur with complaints of black fungal infection. Many of them have lost their sight. Odisha reported its first case of mucormycosis in a 71-year-old Covid patient who also has uncontrolled diabetes. The patient, a resident of the Jajpur district, is now undergoing treatment in Odisha. Madhya Pradesh has detected cases of black fungus and two people have already died in the state. The state has reportedly seen 13 cases of the black fungus. Gujarat has meanwhile reported the highest number of black fungus cases. Gujarat government has started setting up separate wards in hospitals for such patients and has procured 5,000 vials of a medicine used in its treatment. Gujarat has so far reported over 100 cases of mucormycosis, which has left many patients blind. The black fungus infection was first reported during the first wave of the Covid-19 pandemic in India, typically a couple of weeks after

the patient was discharged. However, in the second wave, patients are reporting the infection even while undergoing treatment for Covid-19.

### Treatments of Mucormycosis

**M**ucormycosis may be treated with antifungals, but it will ultimately require surgery. Controlling diabetes, reducing steroid use, and discontinuing immunomodulating drugs are all important, according to doctors. The treatment involves an IV infusion of regular

saline (IV) followed by an infusion of amphotericin B and antifungal therapy for at least 4-6 weeks to maintain sufficient systemic hydration. Experts also emphasised the importance of controlling hyperglycemia and monitoring blood glucose levels during Covid-19 therapy, as well as in diabetics. Steroids should be used with caution - the right timing, dosage, and length are crucial. A major obstacle for clinicians to choose among the current available antifungal agents (Spellberg *et al.*, 2005) in treating mucormycosis is the lack of available clinical trials (Table 1).

Table 1: Antifungal strategies for mucormycosis (Adapted from Spellberg *et al.*, 2005)

Therapy	Anifungal Strategies	Pros and Cons
Established therapies	Amphotericin B(AmB) deoxycholate	Toxicity.
	Liposomal amphotericin B	Less toxic than AmB, Most expensive.
	Amphotericin B lipid complex	Less toxic than AmB.
Investigational/ adjunctive therapies	Itraconazole	Superior toxicity profile.
	Posaconazole	More effective than itraconazole in animal models.
	Caspofungin	Very low toxicity, Virtually no clinical data for mucormycosis.
	Iron chelation	Synergistic with ABLC in murine.
	Hyperbaric oxygen	Benifit in combination with antifungals.
	Cytokine therapy	Nontoxic, Successful case reports, Not widely available.

Mucormycosis may cause the upper jaw and even the eye to be lost. Patients will have to accept the loss of function that comes with a missing jaw, such as trouble chewing, swallowing, facial aesthetics, and self-esteem. If it's the eye or the upper lip, mechanical substitutes or prostheses may be used to replace them. Although prosthetic replacement of missing facial structures will begin once the patient has stabilised following surgery, it is crucial to inform him about the availability of such treatments rather than leaving him to worry about the unexpected loss, which will exacerbate a pre-existing post-Covid stress disorder. Prosthetic reconstruction may be done after surgery, but for better long-term results, intermediate solutions should be prepared even before jaw surgery. Prosthetic repair will help to ensure that the treatment isn't as bad as the disease.

### Conclusion

**T**hough the etiopathogenesis of mucormycosis disease varies from country to country, the disease's presentation can be very aggressive, with a high mortality rate if not treated promptly. As a result, it presents a challenge to many clinicians. With the high mortality rate in mind, the key to

effectively treating this infection is early and timely diagnosis, as well as an effort to recover from the predisposing factors. The condition of this deadly disease can also be improved with early intervention, such as surgical debridement and medications.

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