

**Black Fungus – Mucormycosis: An Overview**Mrs. M. Devi<sup>1</sup>, Assistant Professor, Faculty of Pharmacy, Dr. M. G. R. Educational and Research Institute, Chennai, Tamil Nadu, IndiaRuth J E<sup>2</sup>, Faculty of Pharmacy, Dr. M. G. R. Educational and Research Institute, Chennai, Tamil Nadu, IndiaKanimozhi L<sup>2</sup>, Faculty of Pharmacy, Dr. M. G. R. Educational and Research Institute, Chennai, Tamil Nadu, IndiaChandralekha K<sup>2</sup>, Faculty of Pharmacy, Dr. M. G. R. Educational and Research Institute, Chennai, Tamil Nadu, IndiaMail id: [devibabu03@gmail.com](mailto:devibabu03@gmail.com)**ABSTRACT**

A disease is a particular anomalous condition that will distinctly alter the structure or function of the entire organ or the part of an organism. Infectious diseases were usually caused by microorganisms such as bacteria, viruses, fungi or parasites. Chicken pox, Tuberculosis, Malaria, Sexually transmitted diseases, Tetanus, Candida auris, Aspergillosis, Athletes foot etc. are the common infections occur in human population. There are million species of fungi live in the dirt, on plants, on household surfaces and on skin of animals and human beings. Irritation, Scaly skin, swelling, blister and itching are the some of the clinical manifestation of fungal infections. Black fungus that belongs to the Mucoraceae family usually will tend to cause mucormycosis. Mucormycosis occurs in rare condition to the people who have low immunocompetence and those who are prone to get easily affected by infections. In recent times, Covid 19 infected patients are mostly encountered by mucormycosis. This review article is focuses on Etiology, Epidemiology of Mucormycosis, Risk factors, Clinical manifestations, Diagnosis, Treatment of Mucormycosis and the relation between Mucormycosis and Covid 19.

**KEY WORDS:** Disease, Infection, Fungus, Black fungus, Mucormycosis, Covid 19**INTRODUCTION:**

The infections that are caused by the Black fungus, also known as mucormycosis, are not common, but in recent years they have spread widen and are life-threatening infections. Formerly it was known as Zygomycosis. They turn up with distressing disease symptoms and with various clinical manifestations. Fungus have complex metabolism, the enzymes that were produced from the fungus are noxious. The sporangiospores which were released from them are allergens. Mucormycosis species are saprophytic, usually found in soil, decomposed matter, stored grain, rotten vegetables, fruits etc. Mucormycosis species has a septate or septate ribbon-like hyphae with the right-angle branching. In 1885 Paltauf was the first person to describe the upper airway mucormycosis and coined the term mycosis. In the year 1955 Harris reported the first cure of mucormycosis. <sup>[1][2]</sup>

**TAXONOMY:** <sup>[3]</sup>

KINGDOM	Fungi
PHYLUM	Glomeromycota
SUB-PHYLUM	Mucoromycotina
CLASS	Zycomyces
ORDER	Mucorales
FAMILY	Mucoraceae
GENUS	* Rhizopus                      * Mucor

**MAJOR GENUS-SPECIES NAME:** <sup>[4], [5]</sup>

Rhizopus species	<i>R. arrhizus</i> ( <i>R. oryzae</i> ) <i>R. rhizopodiformis</i> <i>R. azygosporus</i> <i>R. stolonifera</i> <i>R. schipperae</i> <i>R. microsporus</i> var. <i>microsporus</i> <i>var.rhizopodiformis</i> <i>var.oligosporus</i>
Mucor species	<i>M. racemosus</i> <i>M. circinelloides</i> <i>M. Ramosissimus</i> <i>M. indicus</i> <i>M. hiemalis</i> ( <i>Entomophora coronata</i> )
Rhizomucor species	<i>R. pusillus</i>

**OTHER GENUS:**Basidiobolus: *B. ranarum*, (*B. haptosporus*)Conidiobolus: *C. coronatus* (*Entomophora coronata*), *C. incongruous*Absidia: *A. corymbifera*Apophysomyces: *A. elegans*Cunninghamella: *C. bertholletiae*Saksenaea: *S. vasiformis*Cokeromyces: *C. recurvatus*

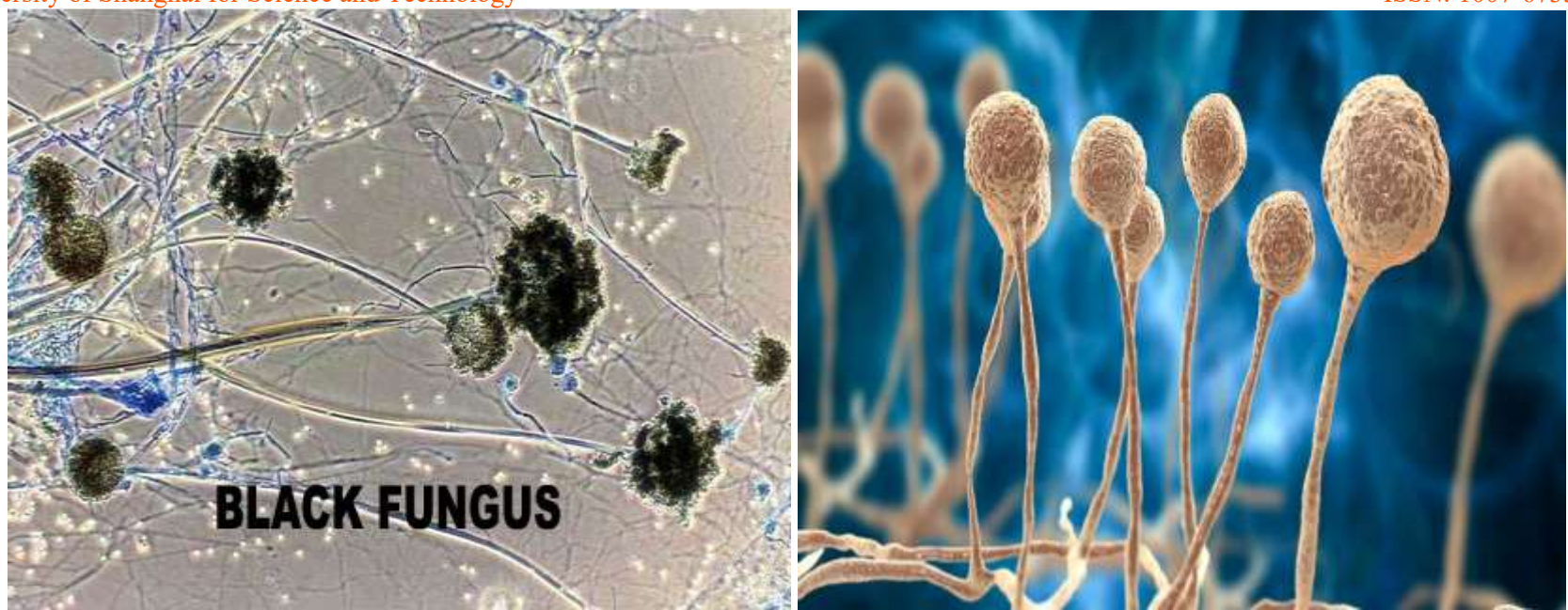


IMAGE 1: Black Fungus

**TYPES OF MUCORMYCOSIS:** <sup>[6]</sup>

- Rhino-orbital/cerebral mucormycosis
- Pulmonary mucormycosis
- Cutaneous mucormycosis
- Gastrointestinal mucormycosis
- Disseminated mucormycosis

**EPIDEMIOLOGY AND PATHOGENESIS:**

Fungus was distributed worldwide, but the breakthrough is high in Europe (34%), Asia (31%), America (28%), Africa (3%), Australia, New Zealand (3%). Over the past 15 years, the number of infected cases reported was increased to twice.. In India, it has been reported that more than 20,000 cases/year, which is the largest encounter of mucormycosis. It has high morbidity and mortality (50% - 85%) which is associated with angio invasive, tissue necrosis, vessel thrombosis fungal infection. One percent of the Patients with less immunity are affected all over the world. The disease is airborne. Individuals with diabetes, metabolic acidosis are the most infected individuals. Inhalation, ingestion, traumatic inoculation are the primary transit methods of mucormycosis infection. After the inhalation, the sporangiospores are settled in nasal turbinates, pulmonary alveoli, paranasal sinuses in the people who are immunocompetent. Later, they induce the interstitial pneumonitis, allergic sinusitis in immunocompromised patients it causes invasive sinus infection and pneumonia. In neonates, it causes mucormycosis when contaminated milk, food was ingested. <sup>[4][6][7][8][11]</sup>

**RISK FACTORS:** <sup>[5][15]</sup>**Major risk factors:**

- Uncontrolled diabetes mellitus in ketoacidosis – 80% to 90% of rhino cerebral mucormycosis
- Iron and aluminum overloaded
- Deferoxamine therapy
- Burns
- Severe trauma like tsunamis, war, tornados
- Protein-energy malnutrition.

**Other risk factors:** HIV/AIDS, other forms of metabolic acidosis, treatment with immunosuppressant drugs like corticosteroids, anti-cancer drugs, organ or bone marrow transplantation, neutropenia, malignancies, prematurity and low birth weight (gastro-intestinal mucormycosis), chronic kidney disease, liver cirrhosis and hepatic failure. Approximately 15-20% of patients have no evidence of underlying conditions.

**CLINICAL MANIFESTATION:** <sup>[9, 10]</sup>

TYPES	SIGNS AND SYMPTOMS	SPECIES RESPONSIBLE
Rhino-orbital/cerebral mucormycosis ( through inhalation of fungi )	Fever, lethargy, headache, orbital pain, abrupt loss of vision, ophthalmoplegia, proptosis, dilated pupil, corneal anaesthesia and clouding, chemosis, peri-orbital cellulitis, sinusitis, epistaxis, facial necrosis and deformation, trigeminal nerve distribution, sensory loss and seizures. Cavernous sinus and internal carotid artery thrombosis	Apophysomyces <i>elegans</i> Rhizopus species
Pulmonary mucormycosis (through inhalation of fungi)	cough, fever, haemoptysis and,or pleuritic chest pain, lymphadenopathy.	Cunninghamella bertholletiae
Cutaneous mucormycosis (severe trauma/direct inoculation)	Pustules, blisters, nodules, necrotic ulcerations, ecthyma gangrenosum-like lesions or necrotizing cellulitis	Apophysomyces <i>elegans</i> Saksenea <i>vasiformis</i>
Gastro-intestinal mucormycosis	nonspecific, and include abdominal pain, hematemesis	Rhizopus species

Disseminated mucormycosis ( spread is haematogenous )	Headache, fever, Visual disturbance, altered mentation	Cunninghamella species
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## DIAGNOSIS:

Primarily, the diagnosis for mucormycosis was made by culturing the organism from tissue histopathology. The medium used is sabouraud-dextrose agar and incubated at 25-37<sup>0</sup>, stains used Gomari methenamine silver, hematoxylin and eosin, periodic acid Schiff, calcofluor white. A Culture test may not be sensitive enough, leading to a false-positive since Mucorales fungi are omnipresent sometimes, it may also be false-negative due to the misleading of a specimen. In histopathology, the last stage of infection emerges a board ribbon-like aseptate mucorale hyphae, which will slightly affect the therapy results. Presently no serology test was done for diagnosis. CT – Computed Tomography could be used for the early detection of pulmonary mucormycosis in cancer patients. In rhino orbital /cerebral mucormycosis affected patients, tissues and serum samples are collected and diagnosed using a semi-nested PCR based assay, amplifying the 18s region of DNA specific to Mucorales. In detecting the circulating Mucorales in infected patients, combinations of quantitative PCR and hydrolysis probes targeting the species were used. Recently developed technologies like Matrix-assisted Laser Desorption / Ionization-Time of Flight Mass Spectroscopy (MALDI-TOF-MS), a molecular diagnosis like real-time PCR (polymerase chain reaction) were also used for diagnosis. Using multiplex real-time – PCR (MRT-PCR), the DNA of numerous species of Mucorales could be detected. [11][12]

## TREATMENT:

Approaches in treating mucormycosis:

- Surgical methods
- Antifungal therapy
- Strategies that reverse risk factors of mucormycosis
- Adjunctive therapies

After radical surgery, 90% of the patients are achieved local control of infection. The liposomal amphotericin B (L-AMB) is preferred over the conventional amphotericin B formulation which causes nephrotoxicity if taken in higher doses. Along with L-AMB, triazoles like Posaconazole and Isavuconazole, which has a broad-spectrum, can be used orally. Mucorales shows resistance to echinocandins, combinational therapy of L-AMB and echinocandins shows synergic action. Combinational therapy of liposomal amphotericin B and caspofungin acetate were found to be effective in the case study of 41 diabetic patients with rhino orbital/cerebral mucormycosis. By conducting In-vitro studies, the drugs like 1-tetrazole fungal specific 14  $\alpha$ -lanosterol demethylase (CYP 51) inhibitor, manogepix and its prodrug fosmanogepix were found to be effective against infections in mice models affected with Rhizopus species. Adjunctive therapies like Hyperbaric oxygen at 2atm pressure for 90 minutes twice a day, cytokine therapy in hematological malignancy, nivolumab, lovastatin, iron chelators like deferasirox could also be used.<sup>[6][13][14]</sup>

## LINK BETWEEN COVID AND MUCORMYCOSIS

COVID-19 is a respiratory disease caused by the SARS-CoV2 virus which was newly discovered. People infected with the COVID-19 virus will suffer from mild to moderate respiratory illness and recover without any special treatment. Older people with primary medical problems like cardiovascular disease, diabetes, obesity, hypertension, chronic respiratory disease, cancer and those who consume immunosuppressant drugs are more likely to develop severe illness.<sup>[18]</sup> Doctors believe that, the overall mortality rate mucormycosis was found to be 50%, and have been aggravated by the use of steroids, which act as a life-saving treatment for critical Covid-19 patients. The use of steroids will reduce the inflammation in the lungs for Covid19 infected persons, and it stops some of the devastations that will happen when the body's immune system is fighting over coronavirus. On the other hand, they also decreases immunity and increases blood sugar levels in both diabetics and non-diabetic Covid-19 patients. It is believed that this drop in immunity level could be provoking these cases of mucormycosis.<sup>[19]</sup>

## EPIDEMIC HITTING OF MUCORMYCOSIS IN INDIA

The Indian Council of Medical Research issued an recommendatory about the risk of black fungus. It noted that five states in India had announced an epidemic, and cases were expected to be diagnosed. In many cases, the patients inhale the mould, which is omnipresent in soil. When it was inhaled, the mould moves to the brain. In some more severe cases, the eye or sections of the skull were taken out to save the patients.<sup>[18]</sup> A total of 45,432 cases of mucormycosis have been reported by all the states in India till July 15 2021 and 4,252 have died<sup>[19]</sup> According to the Centers for Disease Control and Prevention (CDC), mucormycosis was considered as life-threatening infection and had resulted on a mortality rate between 46–96 percent based on the seriousness. An epidemic of black fungus is sweeping India in the wake of an acute surge in COVID-19 cases. Experts said the cause is a combination of two factors. These factors might include contaminated oxygen equipment and the use of steroid drugs to treat certain COVID-19 patients.<sup>[22]</sup>

Steroids can crackdown the cytokine storm (excessive immune response) correlated with Covid-19, eventually decrease the immune system's activity by increasing the blood sugar levels. Dr. Ashraf Ibrahim, a professor of medicine at the University of California, Los Angeles, stated that ill controlled diabetes and practice of using corticosteroids have resulted in risk factors for more diseases. Prevailing environmental factors in India also one of the reason liable to Mucormycosis. "Before Covid-19, population-based studies were conducted and predicted that the load for spread of the disease is 70-80 times higher than all over in the world, "So we cannot opt that diabetes and steroids were the major one, but also exposure to the spores of some causative agents."<sup>[23]</sup>

A 2009 review of research into hospital outbreaks identifies ventilation systems, contaminated bandages or medication patches, intravenous catheters, wooden tongue depressors, adhesive bandages, and ostomy bags are some of the causes for spread of infection. Contamination of foreign substances in air also involved in widespread of infection<sup>[22]</sup>. Prolonged ICU stays and irrational use of broad-spectrum antibiotics, Breakthrough infections in patients on Voriconazole (anti-fungal drug) prophylaxis also increases the risk of developing Mucormycosis in Covid patients.<sup>[24]</sup>

## MANAGEMENT OF MUCORMYCOSIS IN COVID 19 PATIENTS<sup>[25, 26]</sup>

Mucormycosis was treated with anti-fungal medicines which were administered intravenously. These medicines generally include amphotericin B, Posaconazole or Isavuconazole. The medicines were suggested to be given for a few weeks until the growth of fungus was completely inhibited. Oral antifungal drugs were also prescribed.

The Drug Controller General of India (DCGI) has authorized that Liposomal Amphotericin, antifungal medication which is used for treating Mucormycosis in patients.<sup>[25]</sup>

Timely initiation of treatment reduces mortality. The multidisciplinary Team approach is required. Treatment of Mucormycosis involves the combination of surgical debridement and antifungal therapy.<sup>[26]</sup>

Liposomal Amphotericin B in an initial dose of 5mg/kg body weight (10 mg/kg body wt in case of CNS involvement) is the drug of choice. Each vial contains 50 mg, which should be diluted in 5% or 10% dextrose; it is incompatible with normal saline/ Ringer Lactate. This procedure had to be continued till positive response is achieved and disease was stabilized. Later, after several weeks, the schedule includes Posaconazole (300 mg delayed-release tablets twice a day for one day followed by 300 mg daily) or Isavuconazole (200 mg one tablet three times daily for two days followed by 200 mg daily) can be taken orally.

The therapy should be continued until the settlement of signs and symptoms of infection and also involved in eliminating some of the prime risk factors such as hyperglycemia, immunosuppression etc. It may be given relatively long period.

Conventional Amphotericin B (deoxycholate) in the dose 1-1.5mg/kg could be given if the liposomal form is not available and its renal function and serum electrolytes were monitored within normal.

However, in most cases, mucormycosis requires surgery in-order to remove the infected tissue which shelters the fungus. Mucormycosis causes ischemic necrosis (dead tissue by clogging the blood vessels). Hence it is necessary to get rid of the dead tissues. Many procedures may be required to achieve this.

## CONCLUSION

Fungal infections are more common and generally mild, but in sick patients and immunocompromised patients, it can cause severe diseases like Mucormycosis etc. Some antifungal drugs were probably used for treating mild infections. Critical cases can increase the mortality rate. Maintaining a proper health like controlling of blood glucose level, proper use of anti-biotics, anti-fungal drugs, clear explanation of co-morbid conditions and medications to the physician, maintaining of personal hygiene, early detection were important to reduce the risk of mortality. There is a need for more research in the field of mucormycosis to get new treatment regimen to outbreak more and more death records. The information summarized in this review may helpful for researchers to discover new drugs to eradicate Mucormycosis in the entire world. This review may serve as a reference for research hunters and microbiologists to find new lead compounds.

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