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REVIEW ARTICLE OPEN ACCESS

# A Role of Black Fungus in COVID-19: A Review

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## Abstract

**Mucormycosis is a rare type of fungal infection commonly known as zygomycosis, the infection tends to crop up more commonly in individuals with low and weakened immunity level, if left untreated, the mucormycosis can be life-threatening and fatal. Mucormycosis previously known as zygomycosis is a consequential type of infection caused by several mildews known as micromycetes. The revised taxonomical studies revealed that the micromycetes causing the infections are classified as the species of phylum Glomeromycota, class Glomeromycetes, subphylum Mucoromycotina, order Mucorales. The genera of Rhizopus, Mucor, Lichtheimia, Cunninghamella, Rhizomucor, and Apophysomyces, constitute the causative agents of the majority of cases of mucormycosis. The angioinvasive type of disorder caused by mucormycosis is further classified as Mucorales. The patients with Diabetes ketoacidosis and diabetes mellitus are at high-risk factors, followed by the patients with organ transplant, immunocompromised disease, and malignancy. The route of exposure to Mucormycosis may be through the wounded infection that can be pneumonic, or dermal in origin. In the ectodermal form, the fungal organism can invade the skin through open or puncture wounds, or the laceration on the skin. However, the infection has a high mortality rate, the key to successful treatment is early diagnosis, and administration of antifungal drugs, with extensive therapy, followed by surgical debridement of the infection. The morbidity and mortality rate are still at a high number, due to the negligence of the patient to seek medical treatment. Hence the early diagnosis and treatment with antifungal drugs with surgical debridement is a must. The efficacy of oral and venous formulations in the treatment of mucorales is still under debate. Despite the aggressive therapy, the mortality rate is increasing worldwide. The studies have to be conducted to invent the fastest treatment protocol for the treatment of Mucormycosis.**

**Keywords:** Phylum Glomeromycota, Fungal Infection, Mortality, Morbidity, Mucormycosis

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## INTRODUCTION

Mucormycosis is a rare type of fungal infection that tends to occur more commonly in individuals with low and weakened immunity, if left untreated, the mucormycosis can be life-threatening and fatal. Mucormycosis previously known as zygomycosis is a consequential type of infection caused by several mildews known as micromycetes. The revised taxonomical studies revealed that the micromycetes causing the infections are classified as the species of phylum Glomeromycota, a class of Glomeromycetes, subphylum Mucoromycotina, order Mucorales. The genera of Rhizopus, Mucor, Lichtheimia, Cunninghamella, Rhizomucor, and Apophysomyces, constitute the causative agents of the majority of cases of mucormycosis. Mucormycosis is an invasive type of disease caused by the mucormycetes further classified as Mucorales. The Mucorales are mainly saprophytic rapidly growing and can grow and sustain at 37°C or higher temperatures. The molds of an organism are supposedly omnipresent, largely observed in organic dopant, comprising decayed fruits, vegetables, crops and debris, the soil between growing seasons, compost piles, and the excreta from human beings and animals. The existence of non-septate hyphae is a typical form with a fragile structure and is responsible for rapid growth. While the terms mucormycosis, phycomycosis, and zygomycosis are the terms commonly used to refer to the diseases caused by the order Mucorales, the recently revised and addressed term is Mucormycosis (Ibrahim AS et al)[1]. The mucormycosis is one of the most unscrupulous and expeditiously spreading, fatal forms of the fungal disease reported in 1885 in the human species by a German pathologist. The Rhizopus being the lethal variant may cause 90% of disorders involving the head and neck region (Singh AK et al)[2]. These organisms may enter the human body through inhalation, or cuts and open wounds. The Mucorales have been observed in the moist environment in the human body, especially in the mucosal lining of the nasal cavity, oral cavity, and the lining of the pharynx of healthy individuals with no clinical signs and symptoms of infection. Invariably these microbes get more aggravated when the immunity level of the individual goes below average, hence these types of microbes are known as opportunistic organisms that will affect immunocompromised individuals (Pilmis B et al)[3]. The invasion of the microbes within the lateral wall of blood vessel streams results in the formation of a thrombus, which may lead to stagnation of arterial supply causing the necrosis of the associated tissue. The most common type of disorder is seen in the head and neck region, especially the maxillofacial region is commonly known as rhinocerebral mucormycosis, with the widespread involvement of the complete maxillary arch including hard and soft tissue, nasal floor, and, paranasal sinuses including the orbital cavity and central nervous system (Mallis A et al)[4]. The initial symptoms of the disease include cellulitis along with nasal inflammation and periorbital edema, followed by the aggressive type of necrosis of the entire oral cavity. The prompt conservative management followed by surgical intervention has to be done to stop the widespread of fungi to the upper limb resulting in thrombosis that may cause septicemia following multiple organ failures leading to very high morbidity and mortality rate (Branscomb R et al)[5]. It is possible that increased awareness and training of the clinicians, combined with the active involvement of dental healthcare professionals, has contributed to the stabilized reports of the infection (Prakash H et al [6], Raghavendra Rao M et al.[7]). The article reviews the basic cause, diagnosis, and management of mucormycosis.

## DISCUSSION

The mucormycosis shows up as an awful kind of infection that manifests as an infection of the brain, lungs, gastrointestinal, dermal, or diffused form. The most probable route of infection may be the infection of the maxillary sinus following the development of mucormycosis, the palatal involvement will be the first presenting sign that led to the diagnosis of mucormycosis and might be consequently the original cause of the dental pain (Huggins JL et al)[8]. The initial symptoms of mucormycosis involved in the sinus are sinusitis and facial and/ or periorbital cellulitis. The investigative findings may reveal the black gangrenous ulceration related to the invasion of the cells into the bloodstream following the

**Table 1.** Historical Summary of the Nomenclature of Mucormycosis and Entomophthoramycosis

| Disease Name | Author(s) | Date of Publication |
|---|---|---|
| Mycosis mucorina | Platauf | 1985 |
| Mucormycosis | baker | 1957 |
| Phycomycoses | Kian Joe et al. | 1959 |
| Mucormycosis and Entomophthoramycosis | Clark | 1968 |
| Zygomycosis | Ajello et al. | 1976 |
| Mucormycosis and Entomophthoramycosis | Kwon-Chung and Bennet | 1992 |

formation of the blood clot and thrombosis, earlier review reported palatal or gingival necrosis within 72 hours of the onset of the infection in only 14% of cases (Nicolatou-Galitis O et al)[9]. The Historical nomenclature of Mucormycosis is mentioned in Table 1. The zygomycete is a type of mucormycosis that is caused by a mucorale produced by branching of the hyphae that replicates by the formation of zygospores through the lascivious process. The pathogen habitats in the decomposed fruits, feces, and putrid soil. They can also cultured from the rima oris, nasal antrum, and esophagus of healthy disease-free individuals (Kwon-Chung KJ, et al)[10]. The Mucorales are angio invasive in nature leading to tissue necrosis, following disseminated form and fatal in nature, especially in immunocompromised hosts the major reason being the high prevalence rate of immunocompromised disorders, the number of patients at risk for this deadly infection is increasing. These organisms are found ubiquitously and can be commonly observed on manure, plants, ground, and decomposing material. These organisms may not cause illness in most healthy individuals, although mucormycosis is a type of opportunistic deep fungal infection more commonly seen among people with a low immune system. The common path of exposure may be the infection related to the dermal or pulmonic origin. In the ectodermal form, the fungal organism can invade the dermis through unlatched or punctured wounds. The rich vascular supply of the head and neck region usually prevents the fungal infection, although the fungi with virulent performance turn into a lethal disease with a high rate of mortality. The infection caused by these fungi is more

**Table 2.** The various diagnostic tools that may be used in diagnosing the Mucormycosis.

| Methods of Identification | Remarks |
|---|---|
| Direct microscopy | Using KOH wet mounts |
| Fluorescent direct microscopy | Using fluorescent brighteners like Blankophor and Calcofluor White with KOH |
| | ELISA |
| Serology | Immunoblots |
| | Immunodiffussion tests |
| Histopathology | Biopsies of affected tissues |
| | Bronchopulmonary lavages |
| | Identification of genus and species are possible. |
| Culture | Grow on any carbohydrate substrate |
| | Colonies appear within 24-48 hrs |
| | DNA sequencing of ITS region |
| Molecular methods | PCR, qPCR, nested PCR can be done. |
| | Conventional PCR |
| | Restriction fragment length Polymorphism analysis (RELP) |

aggressive and may uncompromisingly progress resulting in the expiration of the individual unless treated with surgical debridement of the infection followed by antifungal therapy. The mucormycosis may become a life-threatening infection in immunocompromised patients that may be caused due to diabetic ketosis, organ grafting, and/or high serum levels of iron, neutropenia. The Diagnosis and initiation of therapy are the most critical measures as these may be due to the acute fulminant nature of the infection majorly caused by the angioinvasive type of fungi. According to Islam MT, et al[11] the various diagnostic tools that may be used in diagnosing the Mucormycosis are mentioned in Table 2. These microorganisms grow at very variable temperatures that may not be virulent; the microorganisms are aerobic, and more commonly seen after two to five days of the incubation period on Sabouraud medium. The tissue necrosis due to invasion of blood vessels and subsequent thrombosis are the classic features of this disease, leading to rapid progression. This disease is rare representing 0.7% of invasive fungal infections, commonly seen in

40%-50% of patients with low immunocompromised state, that may be seen in diabetic patients as well as patients with other risk factors of drug addiction of coagulopathies after an organ transplant. (El-Herte RI[12], Rajashri R[13]) However, the incidence of mucormycosis in apparently immune-competent patients is rarely documented. The infection has a high mortality rate, the key for successful treatment modality is early diagnosis, and administration of antifungal drugs, with extensive therapy, followed by surgical debridement of the infection (Madan R et al[14], Nicolatou-Galitis O et al[9]). Despite the aggressive therapy, the mortality rate is increasing worldwide. New proposed action to stop and prevent the fungal infection is a must, such strategies can be eased by a clear comprehension of the pathogenicity of the disease. The deep invasion of the infections is most commonly characterized by the dissemination of pathogens to the deeper tissues usually associated with aggressive clinical presentation such as mild ulceration to deep perforation into the surrounding tissues and bony areas. The culture method to identify microbial isolation, and antifungal susceptibility provides the standard measure of therapeutic care as quoted by Rajendra Santosh AB, et al[15]. The clinical examination and culture method can play an important role in the diagnosis of fungal infections. The computation with differential identification of a white lesion that is scrapable in nature is an endorsed sampling technique for orally mutated mycosis by collecting the saliva sample, rinsings, scraping of the lesion/smear, the dampened swab, pus, and inflammatory collection from the agile wound as stated by Sanath AK et al[16], Choudhary P et al[17]. The dampened and moistened swab collected is the best-suited method for the swabbing of oral fungal lesions that occur on the mucosa of the lips, circumoral skin tissue, tongue, and other parts of the oral cavity. The serological tests can be the best techniques but have not been instituted yet, that may be assisted in diagnosing the mucormycosis. An increase in glucose level stimulates the proliferation of the fungi, following the reduction in endocytosis and scavenger cell efficiency that permit the otherwise innocuous microorganisms to flourish in the acidic environment as stated by Bakathir AA et al[18], Oswal NP et al[19], Pilmis B et al[3]. The literature studies revealed that the diabetic ketosis fleetingly changes and deranges the potentiality of the iron binding capacity to bind the iron component and alter that may eliminate a significant host defense reaction and permits the growth and development of the Rhizopus oryzae (Bhatt K, et al[20]) concluded, the triumphant treatment modality for mucormycosis is largely dependent on the early diagnosis with all the precautionary measures that include all the underlying predisposing disorders followed with the medicinal treatment options by administration of the antifungal(broad-spectrum) drug therapy with surgical treatment modality followed with debridement of the infected wound. The surgical debridement of the diseased wound should be based on an emergency treatment protocol that can be more advantageous as it may incarcerate and seize the invading the fungi into more into the deeper part of the tissues as mentioned by Salisbury III PL et al[21], Auluck A et al[22]. The most recommended treatment for Mucormycosis is with the broad spectrum antifungal drugs that include Amphotericin B deoxycholate with a maximum tolerated dose that may range from, 1 to 1.5 mg/kg/day. The side effects like nephrotoxic and acute infusional toxic effects of the higher dose of the conventional Amphotericin B drugs can be avoided by lowering the dose that may be continued for a longer duration of time. The commonly advised conventional azoles, which include the voriconazole and fluconazole, do not affect the activity of Zygomycetes fungi. Posaconazole, an orally existing wide-spectrum triazole can be administered at a higher dose of maximum of 800 mg/day in divided doses, and may possess effective antifungal activity. The maximum span of treatment duration is not known, although the decisions for the treatment may be modified to treat the particular stage of the disease. The treatment with an increased level of oxygen pressure (Hyperbaric oxygen therapy), seems to improve the activity of neutrophil cells that may kill microorganisms. The treatment of the mucormycosis with the Hyperbaric oxygen therapy may have an oxidative mechanism of action of the Amphotericin B. The Hyperbaric oxygen therapy, should comprise the exposure to 100% oxygen, each dive ranging from one hour 30 minutes to 2 hours with a maintained pressure from 2.0 to 2.5 atmospheres with minimal exposure of one or two

doses per day for forty number of treatments. The Information regarding the treatment of Mucormycosis with oxygen therapy is sparse and maybe its role is controversial according to Garg D et al[23], Oswal NP et al[19]. The Covid-19 infection causes a severe acute pulmonary syndrome that has been associated with multiple ranges of unscrupulous bacterial and fungal organisms. Recently, the case of the lethal mucormycosis is discern in the patients who recovered from covid-19. The prime cause that appears to facilitate the deadly Mucorales spores to develop and germinate in the people with the covid-19 disease is due to an ideal environment with a very low level of hyperbaric oxygen saturation level, with new onset of the higher glucose level and steroid induced hyperglycemic disorder, the acidic medium, the diabetic ketosis, and increased level of iron with decreased activity of phagocytic cells due to immunocompromised state of the patient coupled with other health disorders may be risk factors that include the prolonged hospitalization with or without ventilators (John TM, et al).[24] Established that the bacterial/fungal organisms can spread in hospital environments via the breath or the hands of healthcare workers, or by the types of equipment installed in hospitals that may not be well sterilized. Mucormycosis is considered to be the most opportunistic disorder. The removal or debridement of the wounded tissue utilizing surgery has to be extensively done, involving all the necrosed tissue that follows the repeated surgical procedures should be recommended to control and improve the outcomes in locally invaded infections. The literature studies on animals that are preferred for observing the efficacy of Liposomal amphotericin B and amphotericin B lipid complex are more dependent on the dose of 10 mg/ kg administered which yielded the best outcome results. However, the serum creatinine levels observed were high in 40% of the cases. The creatinine levels were normalized in almost the 63% of the individuals in 90 days, with 45% of cases responded well. The epidemiological survey on the number of case reports that were issued in between the year 2019- 2021 in the PubMed indexed database information about the risk factors, case presentations, and the diagnosis, treatment modalities, and outcome of the Mucormycosis disorder association with coronavirus demonstrated 47 number of reported cases from which 41 cases had well-documented mucormycosis with coronavirus were observed by Hoenigl M, et al[25], Sen M, et al[26]. The first-line antifungal therapy with broad spectrum antifungal drugs is still under debate, that can be determined on an individual basis and can be adjusted based on the underlying health condition of the individuals.

## CONCLUSION

The Mucorales are the fungi that are normally not virulent, they become more pathogenic when the host immune resistance system is in an exceptionally low and immunocompromised state. An early diagnosis with administration of broad-spectrum antifungal drugs following surgical debridement of the infection is a must. The efficacy of injectable or oral formulations in the treatment of mucormycosis is still debatable. Future randomized controlled studies need to be conducted to assess the most effective and efficacious protocol in the treatment of mucormycosis.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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None.

## DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

## ETHICS STATEMENT

Not applicable.

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