Current Trends in Pharmaceutical Research, 2021 Vol 8 Issue 1
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2582-4783 (Online)

A COMPREHENSIVE REVIEW ON MUCORMYCOSIS (BLACK FUNGUS) AND ITS ASSOCIATION WITH COVID-19

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Abstract

Background: *Mucormycosis is an infection caused by a group of filamentous molds belong to order Mucorales and class Zygomycetes. Mucormycosis is commonly known as black fungus disease. This infection mainly targets diabetic and immune-compromised patients. As COVID-19 infection declines the immunity of patients, so mucormycosis cases are also increasing due to inhalation of molds containing industrial oxygen.* ***Objective:*** *The main objective of the present article is to provide a comprehensive review on mucormycosis, its epidemiology, pathophysiology, diagnosis, treatment, and its association with COVID-19.* ***Methods:*** *An extensive literature search were carried out in various search engine like PubMed, Google Scholars, Research Gate, SCOPUS by using keywords like Mucormycosis, Black fungus, Mucorales, Zygomycetes, Rhizopus, etc. between period of March, 2021 to June 2021.* ***Discussion:*** *The black fungus disease orMucormycosis is a rare invasive fungal infection which has a higher mortality rate if not diagnosed well. The vascular tissue of endothelial cells is common target of Mucorales. There are six forms of Mucormycosis based on anatomical localization such as rhino-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. Patients on treatment for iron overload are more prone to get black fungus.* ***Conclusion:*** *The diagnosis and treatment of mucormycosis are typically difficult based on imaging analysis, sputum culture, bronchoalveolar lavage culture. Treatment with Amphotericin B and appropriate surgery can increase the survival rate up to 1.5 folds. Mucorales possess a certain range of resistance to common antifungal agents. Although, Amphotericin B, Posaconazole, and isavuconazole are possible first-line treatments. COVID-19 infected patients with black fungus are receiving first-line antifungal drugs to mitigate the infections. Much more research needed for the discovery of new drug therapy in the coming future.*

Keywords: Mucormycosis, Black fungus, COVID-19, Mucorales, Zygomycetes, Rhizopus, Amphotericin B, Posaconazole.

INTRODUCTION

The human immune system has the capacity to eliminate large number of pathogens. But, owing to overuse of immunosuppressants and corticosteroids, the susceptibility of fungal infection has been enhanced. The pharmacological target for treatment of fungal disease become limited because target site of eukaryotic

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pathogens is similar to that human [1]. Mucormycosis is an infection which is caused by group of molds containing filaments belong to the phylum Zygomycota[2–4].This kind of fungus are mainly growing on decaying vegetables, bread, soil and dust. People come in contact with these molds through inhalation of spores, contaminated food ingestion or inoculation of disrupted skin or wounds [5–9].

After infection, they produce lesion of black colour due to which mucormycosis are also known as black fungus. Data from last two decades revealed that, mucormycosis emerge as terrifying fungal infection with higher mortality rates. Zygomycetes are the class of fungi which causes fatal infection commonly known as zygomycoses and both the Mucorales and Entomophthorales are belong to zygomycetes class of fungi. *Rhizopus, Mucor, Absidia* and *Cunninghamella* are the genera which comes under Mucorales and *Conidiobolus* and *Basidiobolus* are the two genera belongs to Entomophthorales. Most of the human fungal infection caused by Mucorales fungi, hence mucormycosis and zygomycosis are interchangeably used [4,10]. Among all these pathogens, highly pathogenic and most disease-causing pathogen is *Rhizopus oryzae* [11]. Fungi of Entomophthorales order are uncommon and they cause infection in tropical areas only and produce chronic subcutaneous and cutaneous infection. The characteristic of this infection is that, they occur mainly in host with compromised immune system and infection progress locally by infecting adjacent tissues [4,12–14]. Tissue infarction are caused by infection from Mucorales and they are vasotropic in nature. Based on anatomical localization, the mucormycosis of Mucorales are ranges from rhino-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous infection special reference to immunocompromised patients [15–17].

EPIDEMIOLOGY

The chances of occurring mucormycosis is very rare but from last two decades the cases of this infection increase abruptly particularly in Belgium, France, Switzerland and India [3,9,18–20]. According to a report from National Hospital Discharge Database, France identified 35,876 patients with invasive fungal infection (IFIs) were detected in between 2001 to 2010; among which 1.5% of IFIs cases were of mucormycosis itself [18]. 19 cases of mucormycosis were identified in a single-center study in Spain from 2007 to 2015. Similarly, in a tertiary hospital; from Geneva, Switzerland, within 1989 to 2003; 3 cases of mucormycosis were diagnosed while 16 cases were found in between 2003 to 2008 [20,21]. It was found that, people with medication of immunosuppressant and voriconazole were more susceptible to infection of black fungus [20].

The Mucorales are ubiquitous and thermo-tolerant in nature and they become very active with seasonal variation. In a case study from Israel, 16 of 19 black fungus cases of rhino-orbito-cerebral mucormycosis (ROCM) were found to be occur in autumn while in Japan, 6 cases with hematology patient were found be infected during August to September [22,23].This kind of infection in human were resulted from inhalation of fungal sporangiospores, direct inoculation of pathogens through disrupted skin or mucosa. There is a direct relationship of mucormycosis exist between developed and under-develop countries. Generally, it can be observed that only patient with diabetes mellitus, stem cell transplants and hematological complication were infected in developed countries but in developing countries like India, it occurs due in patients with strokes and uncontrolled diabetes [3,4,10]. Since it's an opportunistic pathogen, so they find very easy to affect people with compromised immune system as well as patient with ketoacidosis, burn and trauma patients, patients on iron therapy or chemotherapy [1].

PATHOPHYSIOLOGY

Sporangiospore ingestion or inhalation or inoculation of spores via wounds or trauma, inhalation of saturated oxygen, medical equipment or improper ventilation system are the ways through which black fungus got inside of a patient [9,24,25]. Phagocytes plays an important role in infection of Mucorales. The hyphae and spores of molds which cause mucormycosis can be easily countered by mononuclear or polymorphonuclear phagocytes. Therefore, persons with very low number of phagocytes or impaired phagocytosis function are at greater risk of black function infections[26]. Excessive chemotherapy can lead to development of neutropenia which become a soft target for this mucormycosis. Along with this, patient with defective neutrophil function due to poor controlled of blood glucose level, acidic pH and ketoacidosis hyperglycemia can severely damage motility and phagocytic capacity of neutrophil [27]. Moreover, phagocytic function can also be compromised by over-dose of glucocorticoids due to which they will not be able to kill the ingested Mucorales [1].

The metabolism of iron plays a significant role in pathogenesis of mucormycosis [5,24,28,29]. Mucormycosis have the capacity to extract iron from host for their survival and multiplication as well as to perform various enzymatic activities. *Rhizopus oryzae* was used for evaluating iron sequester activity and it was found that, mucormycosis grow rapidly in iron containing media but very poor growth in serum devoid of iron [30]. Studies revealed that, iron chelator are acts as inhibitor to growth of *Rhizopus* by capturing free iron while some others act as siderophore by transferring iron to fungal cell for their growth, therefore, patient with iron treatment such as deferoxamine for iron overload are more prone to get infected by mucormycosis[31]. Bacteria or fungi used to produce a low molecular weight

molecule called Siderophores which have strong affinity and specificity to chelate iron molecules. Deferoxamine is a siderophore produce by fungi which have strong affinity for iron and they can isolate iron from ferritin and transferrin to used them for living inside host[32]. During intracellular transport, *Rhizopus* use deferoxamine as iron source by induce a receptorwhich further trap deferoxamine-iron complexes and to inhibit the conversion of ferric to ferrous iron[1]. Mucormycosis have a specific mechanism to invade the endothelial cells from vascular system due to which infection got disseminated from one to other parts of the body. During glucose starvation, GRP78 receptors on cell surface got upregulated and acts as receptors for Mucorales in human for destroy the endothelial cells [33].

CLINICAL MANIFESTATION OF MUCORMYCOSIS- TYPE, SIGN AND SYMPTOMS

Based on anatomical localization, the mucormycosis can be divided into 6 forms: (a) Rhino-orbital-cerebral mucormycosis (ROCM), (b) pulmonary, (c) cutaneous, (d) gastrointestinal (GI), (e) disseminated and (f) miscellaneous mucormycosis [34–41]. 929 mucormycosis cases were reviewed by Roden*et al.*; where they had found that common site of involvement was: sinuses (39%), pulmonary (24%), disseminated (23%) and skin and soft tissue infection (SSTI) (19%). In another study, 92 (60%) had pulmonary disease, 6 (4%) had ROCM among 154 malignancy patients[11]. Brief summary of overall clinical manifestation of mucormycosis listed below:

Forms of mucormycosis	**Pathogenesis of disease state**	**Underlying host risk factor**	**Clinical manifestations**	**Mortality rate**	**References**
Rhino-orbital-cerebral	Inhalation of sporangiospores develop paranasal sinuses which can further spread to involve sphenoid sinus, cavernous sinus and brain tissue	Malignancy,Diabetes mellitus, organ transplant	Sinusitis, eye/facial pain, facial numbness, blurry vision, proptosis, headache	50% or may be higher depends on concentration of immuno-suppression	[42,43]
Pulmonary	Pulmonary blood vessel got invaded by hyphae which can further lead to hemorrhage, ischemia, thrombosis, infarction of distal	Under chemotherapy, neutropenia, lung transplantation	Prolonged fever, nonproductive cough, endobronchial lesion result in obstruction of	66% or higher depend on level of immunosuppression	[44–46]

	tissue		airway, hemoptysis		
Cutaneous	Due to direct inoculation of spores into the skin which can further lead to disseminated disease, but chances are very less to occur from internal organ to skin	Trauma/ burn of skin in susceptible host	Gradual onset to invasive one, fulminant disease, can lead to gangrene and hematogenous dissemination	Varies with severity of disease, 25%	[17,47]
Gastrointestinal	By ingestion of contaminated milk, porridge, breads, alcoholic drinks, herbal and homeopathic formulation due to which stomach and colon get affected	Malnourished children, diabetes mellitus, premature baby, immunosuppression.	Appendiceal, gastric, cecal, gastric perforation, neutropenic patient with fever, typhlitis and hematochezia	85%	[11,48]
Disseminated	Mucormycosis from one organ can transferred to other organ through blood, lungs infection is most commonly happening with dissemination	Iron overload, excessive	Depend on the site of infection and intensity of invasion	Can be fatal if deprived of medication	[24,49]
Miscellaneous	Fungal infected/contaminated medical devices, Mucorales contaminated food stuff such as barley, wheat, onions, cottons, sweet potatoes, oranges, honey and tomatoes	Traumatic inoculation during surgery, contaminated medical devices (catheters, adhesive tapes), immunosuppressive patients	Infection of skin, prosthetic valve endocarditis, osteomyelitis, peritonitis, gastrointestinal disease	Depends on site of infection and immunocompromised host	[50]

Diagnosis of black fungal infection or mucormycosis:

Based on imaging studies, bronchoalveolar lavage culture, sputum culture and needle aspirate, it is very difficult to diagnosed mucormycosis [1]. Therefore, to

begin the appropriate diagnostic procedure and treatment, a high index of suspicion is highly required. In case of proven invasive fungal infection, the fungus can be detected mainly by histological analysis or by culturing a tissue specimen from the site of infection or disease. Presence of a host factor (long use of corticosteroids i.e. more than 3 weeks, recent history of neutropenia, within past 3 months treatment with other T cell immunosuppressants etc.), a clinical criterion (tracheobronchitis, CNS infection, sinonasal infection and on imaging studies evidence of presence of lower respiratory tract fungal disease) and a mycological criterion by direct (direct microscopy, cytology or culture) or indirect (antigen or cell wall constituents detection) testing methods are requires in probable invasive fungal infection. If one of the factors i.e. mycological criterion, from all three factors are absent then also the infection is considered as possible invasive fungal infection [51]. For diagnosis of pulmonary mucormycosis, the conventional radiological techniques are not specific [52]. McAdams HP *et al.* from their studies said that in a case report of 32 patients who suffered from pulmonary mucormycosis, they found that homogeneous, progressive, lobar or multi-lobar consolidation without significant lobar predilection were the most common radiological manifestation and lung nodules or masses were less commonly found. In approximately 40% cases cavitation was found [53]. For the diagnosis of pulmonary, rhino-orbital-cerebral and disseminated mucormycosis, higher resolution computed tomography (CT) and magnetic resonance imaging can be highly useful [52]. On CT chest images, mass like or nodules or wedge-shaped consolidation, mainly in the posterior segments of the upper lobes in lungs were seen in 8 patients with pulmonary mucormycosis, whereas presence of endobronchial lesions on CT chest images were very less [54]. In case of pulmonary mucormycosis on CT images, a halo sign i.e. a ground glass opacity surrounding a pulmonary nodule was found, which was associated with 78% of the nodules. A reverse halo sign i.e. a rim of consolidation surrounding a center of ground glass opacity, which is a good indicator of pulmonary mucormycosis was also found on CT images when compared with other pulmonary fungal infections [55,56]. Although direct microscopic examination of paranasal sinus secretions, sputum, bronchoalveolar lavage fluid is often non-diagnostic parameters, but it is useful for isolation of Mucorales organism from any of these specimens in a susceptible host [56]. Mucorales organisms are ribbon-like, broad, irregular shaped, non-septate (or sparsely septate) hyphae with branches arising at 45˚ to 90˚ [57]. Galactomannan (GM) or a specific amount of 1, 3-β-D-glucan (BDG) are absent in the cell wall of Mucorales. Therefore, for diagnosis of mucormycosis neither GM nor BDG assays are helpful [58]. Mucormycosis can be effectively diagnosed by histopathological assessment and culture [56,59]. Significant infarcts and angioinvasive cases are being observe in neutrophilic inflammation, which are revealed by histopathological examination [57]. Mucorales

causes tissue damage of involved organs and shows preference for vascular invasion [5]. In mucormycosis cases, on infected persons a black eschar or dead tissue may be seen as a result of tissue infraction and as blood vessels become thrombosed [60]. Grocott-Gomori methenamine silver is suitable stain for identification of Mucorales, since Mucorales show poor staining with gram stain [59]. Neutrophilic, nonspecific inflammatory changes or granulomatous may be present along with mucormycotic infections. Also, angioinvasion or infarcts may be commonly found in some cases of mucormycosis [61]. If focal pulmonary nodules or masses are present, then fine needle aspiration biopsy may be use for diagnosis of mucormycosis [62,63]. Although the histopathological studies show the presence of characteristic organism, still sometimes culture of organism may show negative results because the grinding of tissue specimen for culture and the rare septations can cause damage to the hyphae of organism, and prevent their growth in culture [64]. In case of mucormycosis although dissemination has occurs, still blood cultures are rarely positive [59]. For diagnosis of some species such as *Mucor, Rhizomucor, Rhizopus, Lichtheimia,* quantitative PCR in tissue or serum can be used which may be than culture technique [56,65–73]. With the advancement of technology now a day's molecular tools have also been developed which can identify mucormycosis directly from the tissue samples; for this purpose, over paraffin-embedded tissue, fresh tissue is preferred since formalin can damage DNA [74,75]. Another tool that have a high accuracy for determinations of mold from cultures are matrix- assisted laser desorption or ionization and time of flight [76]. Also, for detection of invasive mold infections from blood specimens, next generation sequencing can be useful [77].

Conditions prone to get easily infected with black fungal infection/mucormycosis:

There are several health conditions of people who are more prone to developed mucormycosis for example poorly controlled diabetes mellitus, hematological malignancies with neutropenia, solid organ transplant recipients, hematopoietic stem cell transplant recipients, rheumatic or autoimmune disease, chemotherapy or immunosuppression, peritoneal dialysis, human immunodeficiency virus infection, malnutrition, overload of iron in body, burns, trauma and people who used voriconazole as a medication in past [11,78,87,88,79–86]. Jeong W. *et al.* said that a meta-analysis was done from 600 publications, from the year 2000 to 2017, which contains 851 worldwide cases of mucormycosis with the following risk factors such as diabetes mellitus (40%), trauma (33%), hematological malignancies (32%), diabetic ketoacidosis (20%), neutropenia (20%), no underlying disease (18%), solid organ transplant recipients (14%), burns (11%), natural disease (5%) [78]. The most common risk factor for mucormycosis in Asia is diabetes mellitus while in North

America and Europe, organ transplant and hematological malignancies is the most common risk factors [37 [78,89,90]. Here some of the most common risk factors are described below:

Diabetes mellitus:

People with poorly controlled diabetes mellitus which is associated with particularly chemotaxis, innate immunity defects, phagocytosis and macrophages are highly susceptible for acquiring mucormycosis [89,91]. Diabetics in association with ketoacidosis are at higher risk of developing rhino-cerebral mucormycosis [11]. In case of diabetic patients, the common site of infection is sinuses, but it can easily spread to the bone, orbit and brain of the patients [92]. Diabetic patients with organ transplant or hematological malignancies, disseminated or pulmonary mucormycosis infection are very rare [87,93].

Solid organ transplant:

The complication of mucormycosis is generally rare in case of solid organ transplant patients [94]. Based on data from U.S Centers of Transplant-Associated Infection Surveillance Network from the year 2001 to 2006 the annual incidence of mucormycosis in solid organ transplant patients was 0.07% [86]. Song *et al.* said that from 123 articles which were published between 1970 to 2015, they had found 174 cases of mucormycosis in renal transplant patients and overall death rate was 42.5% [95]. Rabin *et al.* said that at the same center among all 362 heart transplant patients only one case of mucormycosis was found from 1995 to 2012 [96].

Hematopoietic stem cell transplant:

In case of hematopoietic stem cell transplant patients mainly with graft versus host disease, mucormycosis can easily occurs [48,97]. A retrospective review at Johns Hopkins Hospital (Baltimore, MD) from 2000 to 2009 for hematopoietic stem cell transplant and solid organ transplant, the cases of mucormycosis was found to be 8.5% of invasive mold infection [98]. Center for International Blood and Marrow Transplant Research collected the data from 66 worldwide transplant centers and they reported 72 mucormycosis cases during the 1st year of post allogeneic hematopoietic stem cell transplant [99].

Use of corticosteroids and rheumatic disease:

Long term use of corticosteroids can damage macrophages and neutrophils and also it can induce diabetes in patients [5]. In case of patients with systemic lupus erythematosus, disseminated mucormycosis is common with higher mortality rate [100]. Other risk factor for opportunistic mucormycosis involves nephritic syndrome, hypocomplementemia, uremia, diabetes mellitus and leucopenia. Also,

opportunistic mucormycosis infrequently occurs in other autoimmune disorders. In case of Wegener granulomatosis, mucormycosis cannot be easily diagnosed [101].

Human immunodeficiency virus (HIV) infection or AIDS:

The cases of mucormycosis in AIDS patients are very uncommon. Antinori*et al.* did a retrospective study from 1984 to 2002, in 1630 autopsies patients and found that only two patients had mucormycosis [102]. Most of the mucormycosis cases are linked with intravenous use of drug in HIV infected patients [103–105].

No underlying disease:

Mucormycosis can also occur in patients with no underlying disease [46]. In this population of patients, primary cutaneous mucormycosis associated with trauma such as surgical trauma (use of contaminated adhesive dressings, bandages, central venous catheters and wooden tongue depressors) and burn are common [106,107].

Chelation therapy with DFO and Iron overload:

In dialysis patients to treat iron and aluminum overload, use of iron chelator and DFO therapy can produce higher risk for angioinvasive mucormycosis [31]. McNab AA *et al.* said that according to a report of an international registry, 78% of dialysis patients who received DFO had mucormycosis. Disseminated mucormycosis is most common in case of patients receiving DFO treatment with 80% mortality rate [108].

Mucormycosis in children:

In children occurrence of mucormycosis is very rare. Zaoutis*et al.* studied all pediatric cases of mucormycosis before 2004 and they found 157 cases, where 64% was male with an average age of 5 years and 28 patients had hematological malignancies and 9 patients had hematopoietic stem cell transplant [109]. Roilides E *et al.* reported another 30 pediatric cases of mucormycosis from the year 2004 to 2008 [110].

Long term use of voriconazole:

The long-term use of voriconazole in case of hematopoietic stem cell transplant and hematological malignancies patients can produce higher risk for mucormycosis [111–113]. Also in place of voriconazole, use of itraconazole or fluconazole in allogeneic transplant patients does not produce the risk for mucormycosis [114,115].

Black fungal infection/mucormycosis in association with COVID-19:

One of the newer problem arising recently in India and also in some other countries is black fungal infection or mucormycosis in COVID-19 as well as post COVID-19

patients. Mucormycosis is mainly arising in COVID-19 patients due to the use of steroids as a medication to suppress highly active immune system, so that it can help COVID-19 patients to protect their lung from damage by a mechanism known as “cytokine storm” [116,117]. Based on the recent scenario of increasing cases of mucormycosis in COVID-19 patients, the physician should keep eyes on their patients even after complete recovery from this disease [117]. By observing the early symptoms of mucormycosis i.e. fever, swelling of one side of the face, black discharge from nasal, pain in head, blockage of nose, teeth weakness, appearance of black patches on nose and upper inner side of the mouth, blurred and weak vision, brain infection, ulceration inside the mouth, breathlessness, pain in chest and redness and loss of sensation in cheeks area in COVID-19 patients physician can identify the infection and give early treatment to prevent the spread of disease to other organs as well as to cure this infection at early stage to decrease mortality rate [117–119]. According to a systemic review report the common form of mucormycosis that is seen in COVID-19 patients are pulmonary mucormycosis, rhino-orbital-cerebral mucormycosis, gastrointestinal mucormycosis and disseminated mucormycosis [120]. Dr. Arunaloke Chakrabarti, department head of Microbiology, PGIMER, Chandigarh opined that there are different causes of mucormycosis in COVID-19 patientsand those COVID-19 patients with uncontrollable diabetes and are also on steroids are at higher risk of acquiring mucormycosis. Dr. Chakrabarti also stated that during the infection of COVID-19, the iron containing ferritin level increases in patient’s body, which is a good precursor for growth of mucormycosis [117]. Another main reason for mucormycosis in COVID-19 patients is use of unsterile oxygen. Black fungus is used to grow in damp areas, it is also found in the inner surface of the water tanks. Hence it is highly important to examine the water used for oxygenation regularly in COVID-19 patients. Also use of sterile canula and oxygen mask is highly important to prevent entry of mucormycosis in COVID-19 patients [121]. In case of COVID-19 patients with organ transplantation, the risk for mucormycosis increases as they are on steroids for immunosuppressive activities. Khatri *et al.* reported a case of mucormycosis associated COVID-19 in a recent heart transplant patient and concluded that even after using broad spectrum anti-fungal medication with surgical intervention, doctors failed to save the life of patient [122]. Sharma *et al.* stated a case report of 23 recently recovered COVID-19 patients who suffered from mucormycosis. All these 23 patients used steroids for treatment of COVID-19 and 21 out of 23 patients were diabetic [123]. In India most common risk factors for mucormycosis in COVID-19 patients is uncontrollable diabetes, the use of steroids during their COVID-19 treatment can also increase the level of glucose which leads to hyperglycemia in patients [124]. According to Dr. Yashwant Ingale, head of dental department YCM hospital, mucormycosis mainly affects maxilla however

mandibular mucormycosis had also been reported [125]. Dr. Akshay Nair, an eye surgeon from Mumbai, in the month of April 2021, opined that he had seen nearly 40 patients of mucormycosis who were recently recovered from COVID-19 and most of the patients were diabetic and 11 of them had to remove their eye for survival. Dr. Nair also remarked that he had to remove the eye from 25 years old mucormycosis patient to save her life. In between the month of December 2020 to February 2021, another 58 cases of mucormycosis associated COVID-19 was reported by six of Dr. Akshay Nair's colleagues in Mumbai, Bangalore, Hyderabad, Pune and Delhi. Another doctor from Mumbai's busy Sion hospital, Dr. Renuka Bradoo remarked that she had experienced 24 cases of mucormycosis in recently recovered COVID-19 patients in past two months, and out of 24 cases, 6 patients lost their life and 11 of them had lost their eyes [126]. Although the use of steroids cannot be stopped in COVID-19 patients but by taking proper care, maintaining hygiene and by early diagnosis and treatment physician can prevent the spreading and severity of infection [127,128].

Treatments related to black fungal infection/mucormycosis:

Early diagnosis is the main key to control mucormycosis. The successfulness of treatments mainly relies on early and timely diagnosis along with prevention of predisposing factors associated with mucormycosis [1]. Prevention of spreading of infection to other organs by surgical debridement of the infected tissue is another method to treat mucormycosis specially in case of rhino-cerebral or soft tissue involvement [57,129]. Early high dose systemic anti-fungal treatment produces greater than 1.5-fold higher survival rates in patients [81,107]. Mucorales are naturally resistance to almost most of the anti-fungal medication, therefore choice of anti-fungal medication is very difficult [130,131]. The main initial therapy for mucormycosis is, the lipid formulations of amphotericin B (LFAB) [57,71]. FDA approved triazole isavuconazole (ISAV) for the treatment of mucormycosis in adult populations while posaconazole also possesses activity against mucormycosis. For induction and salvage therapy both POSA and ISAV are used[132,133]. According to the report of a single-center study in between 1989 to 2006 containing 70 patients of mucormycosis with hematological malignancies with neutropenia, administration of amphotericin B (AmB) based therapy after 6 days of initial infection leads to increase in two-fold mortality rate at twelve weeks after diagnosis of mucormycosis [84]. In case of both safety and efficacy LFAB is always better than AmB deoxycholate. The first line therapy for mucormycosis is always a high dose of LFAB i.e. 5 to 10 mg/kg/day for minimum 6 to 8 weeks [134]. Sun HY *et al.* mentioned that in case of rhino-orbital cerebral zygomycosis in solid organ transplant patients, death rate among patients treated with LFAB was found to be only 15.7% while it was 59.6% in case of AmB deoxycholate treated patients [94].

The effectiveness of POSA and ISAV treatment depends on the genus and species of Mucorales[135,136]. POSA can be administered effectively by oral suspension i.e. 800mg daily by oral route in two or four divided doses, intravenous formulation i.e. 300mg, twice daily by IV route on day 1, then 300mg once daily and also as a tablet i.e. 300mg, twice daily by IV route on day 1, then 300mg once daily. The oral tablet form has high absorption than the oral suspension formulation and is less affected by gastric acid or food suppression, therefore it is more preferred as a treatment [137]. Initial treatment with LFAB followed by sequential treatment with POSA has been used successfully for the treatment of mucormycosis [138].

In United States for the treatment of invasive mucormycosis and invasive aspergillosis in adults ISAV is approved by FDA. Also, when AmB is inappropriate for mucormycosis, the European Medicine Agency approved ISAV to treat this infection [139]. ISAV is administered as a loading dose of 372mg as an isavuconazonium sulfate for every 8 hours of 6 doses, followed my maintenance dose of 372mg as an isavuconazonium sulfate once daily starting from 12 to 24 hours after last loading dose [140]. Therapeutic monitoring is needed while using triazoles i.e. POSA and VORI for treatment of mucormycosis to prevent unwanted adverse effects [141,142]

For those patients who were unable to tolerate AmB, the combination treatment of posaconazole and caspofungin was found to be effective due to potential synergistic effects between two drugs [143]. The combination of caspofungin and higher dose of LAMB followed by strict control of diabetes and long-term hyperbaric oxygen, posaconazole is highly effective in rhino-orbital cerebral mucormycosis when AmB alone failed to produce desired effect [144]. Roden MM *et al.* reviewed 929 mucormycosis cases and said that according to therapeutic approach the rate of survival was found to be 70% in AmB along with surgery, 61% in AmB alone treatment and 57% in surgery alone [11]. SongY *et al.* said that in a cohort study containing 174 mucormycosis patients with renal transplant, the overall rate of survival was found to be higher i.e. 70.2% with AmB and POSA plus surgical debridement, whereas survival rate was 36.4% in surgery alone, 32.4% in anti-fungal therapy alone and 0% in case of no therapy [95]. Another effective treatment for mucormycosis is iron chelators. In murine model of mice with mucormycosis along with diabetic ketoacidosis; deferasirox, an iron chelating agent was found to increased survival rate [29]. Deferasirox along with LFAB is also effective in rhino-orbital cerebral mucormycosis patients [145]. Spellberg B *et al.* said that a randomized trial was done on 20 mucormycosis patients in two groups, one group with LFAB with deferasirox and another with LFAB with placebo. And from their trial they found that the mortality rate at 90 days was significantly more in case of deferasirox i.e. 82% as compared to placebo i.e. 22% [146]. Therefore, a guideline

was made by Sixth European Conference on Infection in Leukemia (ECIL-6) on leukemic and hematopoietic stem cell transplant patients to prevent the use of deferasirox as a treatment for mucormycosis [147].

CONCLUSION

Mucormycosis is a rare invasive fungal invasion which mainly occur in patient with diabetes, immunocompromised and iron overload treatment. Recently, it has been found in the body of SARS-CoV-2 infected patients with higher mortality rate. It has been observed that, due to extensive shortage of sterile oxygen, rapid supply of industrial oxygen was provide to save the patient due to which pathogens of mucormycosis is entered into the immunocompromised patients due which along with COVID-19 they also suffer from black fungus. Therefore, treatment and diagnosed for COVID-19 patients become troublesome. People on treatment for iron overloading such as Deferoxamine are more likely to get affected by black fungus. Among six form of black fungus based on location, rhino-cerebral and pulmonary has higher mortality rate of patients. Since, Amphotericin B was extensively used for treatment, but if it fails then combination of posaconazole and caspofungin was found to be effective due to potential synergistic effects. More reliable and efficient drug therapy are very much necessary to deal with this kind of complex disease.

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How to cite this article:

Alom S, Ali F, and Zaman K Md. A comprehensive review on mucormycosis (black fungus) and its association with covid-19, *Curr Trends Pharm Res,* 2021; 8 (1): 11-40.