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MUCORMYCOSIS: A DETAIL REVIEW

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ABSTRACT

Mucormycosis was previously called zygomycosis. It is a rare angio invasive infection that occurs due to fungi Mucorales with high morbidity and mortality. This infection highly recognizes in immunosuppressed patients. Immunosuppressed states such as hematological malignancy, bone marrow or peripheral blood stem cell transplantation, solid organ transplantation, neutropenia, diabetes mellitus with or without ketoacidosis, corticosteroids, and deferoxamine therapy for iron overload predispose patients to infection. This fungal infection can list as rhino-orbitocerebral, cutaneous, gastrointestinal, disseminated, and pulmonary types. The mortality rate can come 100% depending on the patients underlying disease and the form of mucormycosis. In India, the prevalence of mucormycosis is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population. The main aim and intention of this review are to providing with brief information about the aetiology, epidemiology, symptoms of mucormycosis, fatality of rhinocerebral mucormycosis, along recent advances in diagnostic and treatment.

KEYWORDS: Mucormycosis, Zygomycosis, Pathophysiology, Rhinocerebral mucormycosis, Amphotericin B.

INTRODUCTION

The term mucormycosis was coined by American pathologist R. D. Baker, and it can also be known as zygomycosis. This insidious fungal infection is causing by the members of Mucorales and zygomycotic species.[1,2] Mucormycosis is also called black fungus, can turn serious if not treated on time. Rhizopus species and mucor species both are the most common types that cause mucormycosis.[5] Mucor is the microbial genus of nearly 40 species of molds commonly found in the soil, digestive systems, plant surfaces, some cheeses like Tomme de Savoie, foul vegetable matter, and iron oxide residue in the biosorption process.[3,4,5] Mucormycotina is a very common saprobe which is originating from rotten substances or soils. The infections with Mucorales classify by rapid progression.[1,6] Mucormycosis is classified depending on the clinical presentation as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or other, includes unusual, rare forms, such as endocarditis, osteomyelitis, peritonitis, renal, etc.[59] Inhalation of spores through the mouth or nose or even through a skin laceration is involved in the pathophysiology. Individuals may generate an inadequate response with compromised cellular and humoral defense mechanisms. To the paranasal sinuses and consequently, to the orbit, meninges, and brain by direct extension, the fungus may then spread.[64] Affluent management of this lethal infection requires the early diagnosis of the disease and combative and prompt medical and surgical treatment to prevent the high morbidity and mortality associated with this disease process.[65]

History: The first case of mucormycosis was reported in 1885 by the German pathologist Paltauf, and it describes as Mycosis Mucorina.[7] Mucormycosis was more seen among immune-compromised individuals in the 1980s and 1990s.[6,8] A study was carried out in France based on prevalence rate reported amplification by 7.4% per year.[9] With the possibility of seasonal variation of Mucorales infection occurrence worldwide has been reported.[10]

Aetiology: Mucormycosis is a fungal infection belonging to the order Mucorales.[11,12] The most common organism isolated from patients who suffered from mucormycosis is *Rhizopus oryzae*, and it is responsible for ~70% of all cases of mucormycosis.[13,14] An uncontrolled diabetes mellitus in ketoacidosis is one of the high-risk factors of mucormycosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma, and burns, malignant hematologic disorders, and deferoxamine therapy in the patients accepting hemodialysis.[15,16,17] In the US, the number of patients at risk for this deadly infection is dramatically increasing because of the rising prevalence of diabetes mellitus, cancer, and organ transplantation in the aging

population.[18] In host defense, neutrophils play a significant role against Mucorales; its work is weaker at a different level in diabetes mellitus.[6,19,20]

- **Pathophysiology of mucormycosis:** Mucormycosis include a range of infections produced by *Zygomycetes*, a class of fungi that generate branching ribbon-like hyphae, and the formation of zygospores by sexual reproduction. Omnipresent in fruits, soil, and feces, pathogens can be found and can too be cultured from the oral cavity, nasal passages, and throat of healthy disease-free individuals. A distinct pattern of clinical infection produces by Mucorales is a subtype of *Zygomycetes.* Commonly the fungi are avirulent; only when the host resistance is exceedingly low do they become pathogenic. Especially when the host is immunosuppressed, an extraction wound in the mouth or ulceration in the mucosa can be a harbor of entry for mucormycosis in the maxillofacial region.[62]

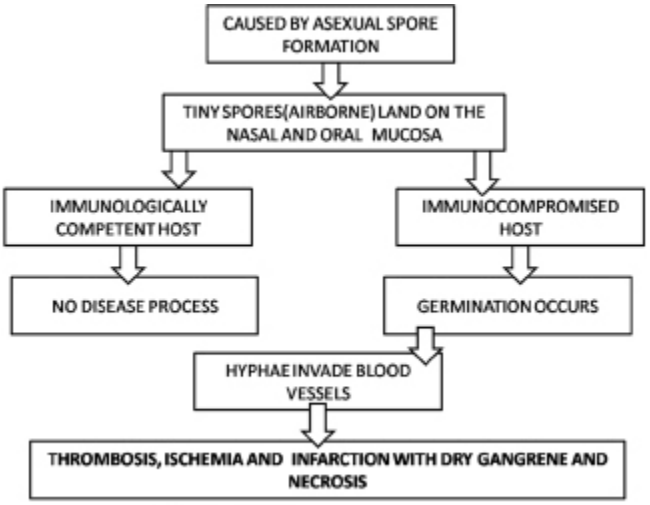


Figure-1: Chart shows pathophysiology of mucormycosis.

By the cause of asexual spore formation, the infection of mucormycosis has occurred. By the asexual spore formation, the tiny spores are forms; spores become airborne and settle on the oral and nasal mucosa of humans. By the phagocytic response, spores will be limited; in the majority of immunologically competent hosts. The germination will follow, and hyphae will develop if this response get fails. In removing the hyphae, polymorphonuclear leukocytes are less effective, the infection becomes established in immunosuppressed individual cases. It moreover improvement as the hyphae begin to invade arteries, wherein they spread within the vessel walls, and lumens generating thrombosis, ischemia, and infarction with dry gangrene of the affected tissues. The results in sepsis can occur by the hematogenous spread to the other organs (lung, brain, and so on).[63]

Epidemiology: Clinical demonstration of mucormycosis is dependent on the patient's fundamental medical condition. The most common form of mucormycosis is rhino-orbito- cerebral mucormycosis (44-49%) overall, is followed by cutaneous (10–16%), pulmonary (10–11%), disseminated (6–11.6%), and gastrointestinal (2–11%) presentations.[29,30,31,32] The most common causes of mucormycosis are the patients with hematological malignancy, pulmonary, followed by disseminated and rhino-orbtio-cerebral presentations.[33] Rhino-orbito-cerebral or pulmonary mucormycosis usually developed in diabetic patients.[31,34] From all corners of the world, mucormycosis cases have been reports. A possible seasonal variation in Mucorales infection has been commenting on by a few papers.[35,36] In Israel, there are 16 out of 19 cases of rhino-orbito-cerebral mucormycosis that occurred between August and November noted by Talmi et al.[36] In Japan, during August and September, a similar seasonal variation among hematology patients with six out of seven cases of pulmonary mucormycosis having developed was noted by Funada and Matsuda.[35]

Signs and symptoms: Mucormycosis generally infects the sinuses, brain, and lungs. The most common forms of mucormycosis are infections of the oral cavity or brain; the fungus can also infect the other areas of the body like the gastrointestinal tract, skin, and other organ systems shown in figure-2. The maxilla may be affected in rare cases by mucormycosis. The fungal infections occurred by mucormycosis are usually prevented by the rich blood vessel supply of maxillofacial areas, although more virulent fungi, like those responsible for mucormycosis, can often overcome this difficulty.[5]

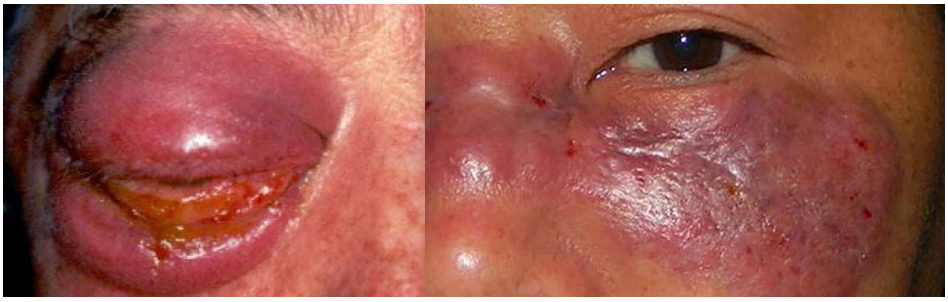


Figure-2: Mucormycosis.

Clinical Presentations and Manifestations: There are two types of infection of mucormycosis are take place in human beings. 1) Superficial and Visceral and 2) Localized and Disseminated. The superficial form occurs in the skin, ear, fingernails, and the visceral form are indicates pulmonary, gastrointestinal, and rhino cerebral types. These spores are entering may take place either through the cutaneous or respiratory route (E.g., the spores are spread during the taking of soiled food or by trained needles).[6,21]

- **Rhinocerebral mucormycosis:** The occurrence of rhinocerebral mucormycosis is 33 - 50%. The presumptive aetiological agent is considering as *Apophysomyces elegans*.[2,23] The infection of mucormycosis starts from paranasal sinuses, subsequent inhalation of spores, and probable expansion to the brain and successively sinuses, nose, and eyes are affected shown in figure-3.

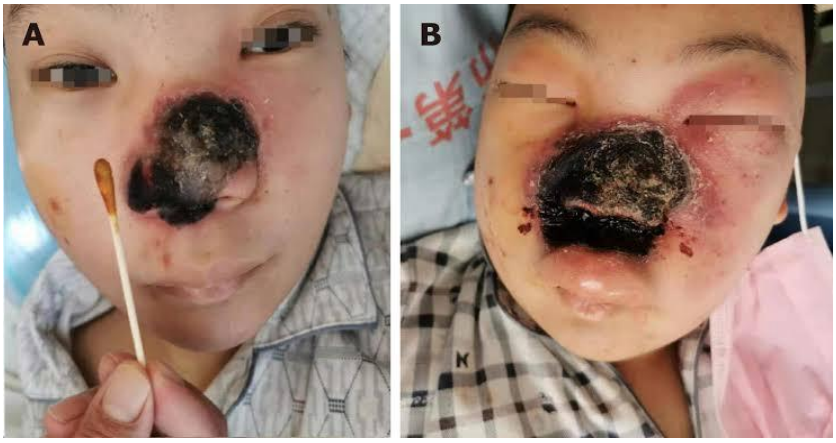


Figure-3: Rhinocerebral mucormycosis.

Its clinical manifestation begins with palatal and sinuses necrosis, further enters the orbit form to get intra-cranial structures. The symptoms frequently included fever, blindness, exophthalmos, nose-bleeding, facial paralysis and attack of the trigeminal nerve, black lesions on nasal bridge or upper inside of the mouth that fast become more serious. The effect of unsettled rhino-sinus mucormycosis is cavernous sinus thrombosis. Also, can be seen the appearance of reddish-black nasal turbinate and septum along with a nasal discharge. The cranial vault leads to blindness, lethargy, and seizures, followed by death as the progression of the disease.[6,21] Mucormycosis infection shows varying clinical appearance with increased incidence of primary skin infection and a significant prognosis predisposed by localization, according to Lanternier et al.[24] The prevalence of mucor infection is around 500 individuals a year in the USA.[25] So, this infection is 10-50 times lesser than candidiasis or aspergillosis.[26] The Occurrence of this infection possibly maybe around 2 - 3% among allogeneic bone marrow transplant patients.[27,28]

- **Pulmonary mucormycosis:** The second most common site of involvement of Mucorales infection is the pulmonary site. The primary route of infection in pulmonary mucormycosis is the inhalation of spores. Compared to other forms of mucormycosis, patients with leukemia, lymphoma, and severe neutropenia remain at greater risk of developing pulmonary mucormycosis. The added risk factor of diabetes may need for the patients with lymphoma to place them at risk for infection. In the rare cases seen that patients with solid tumors develop pulmonary mucormycosis. There is a similar radiographic appearance of pulmonary mucormycosis to aspergillosis. Both infections tend to invade blood vessels and generate thrombosis. Infiltrate, wedge-shaped consolidation, nodule, cavitation, mycetoma, lobar collapse, and, rarely, pleural effusion included in radiographic presentations.[32] In immunocompetent hosts, pulmonary mucormycosis is not normal.[72] Some symptoms present for several months before the diagnosis when the infection in an

immunocompetent host does occur. For example, an immunocompetent patient with *Cunninghamella bertholletiae* pulmonary infection presents a 4-month history of productive cough, fever, chills, and night sweats reported by Zeilender et al.[73] With focal pulmonary infection, a death rate of 60–100% is reporting in hematology patients. Subacute pulmonary type of mucormycosis may be more responsive to medical therapy alone. The most common method of treatment is a combined surgical and medical approach.[32]

- **Cutaneous mucormycosis:** This type of mucormycosis can develop after a break in the skin's integrity from surgery, burns (shown in figure-4), soiled trauma, motor vehicle accidents, bone fractures, intravenous lines, insect bites, cactus spine injuries, abrasions, lacerations, biopsy sites, allergen patch testing, contaminated adhesive tapes, and intramuscular injections.[74]

Figure-4: Cutaneous Mucormycosis.

Diabetes, leukemia, and organ transplantation are including as the predisposing factors.[75] Diabetes was present in only 26% of cutaneous cases, compared to 67% of rhinocerebral, 21% of disseminated, and 20% of pulmonary infections shown in the review by Adam et al. Leukemia and neutropenia are observing in 16% of cutaneous, 16% of rhinocerebral, 42% of disseminated, and 48% of pulmonary infections. This type of mucormycosis can manifest as a superficial or deep infection.[76] Cutaneous mucormycosis can appear as pimples, blisters, nodules, necrotic ulcerations, ecthyma gangrenosum-like lesions of necrotizing cellulitis. Diagnosis required a skin biopsy.[77,78] As compared to the other forms of mucormycosis, cutaneous mucormycosis portends a better prognosis. Cutaneous involvement had the lowest mortality (16%), compared to 67% for rhinocerebral, 83% for pulmonary, and 100% for disseminated and gastrointestinal mucormycosis mentioned in a review of the medical literature. From indolent to a rapidly progressive infection requiring surgical debridement, antifungal therapy, or even amputation cutaneous mucormycosis, presentation are varies.[76]

- **Disseminated mucormycosis:** Two or more noncontiguous organs are involved in disseminated mucormycosis. The majority of patients with disseminated mucormycosis comprise neutropenic patients with leukemia or lymphoma.[77,78] In 23–62% of cases with hematological malignancy, dissemination arises. Organ transplantation, chemotherapy, corticosteroids, and deferoxamine therapy includes as other risk factors for dissemination.[33,77] The death rate for disseminated disease approaches 100%.[79]

- **Gastrointestinal Mucormycosis:** Abdominal pain, haematemesis, and melena are the nonspecific signs and symptoms of gastrointestinal mucormycosis.[80,81] Gastrointestinal mucormycosis have developed in the patients who have undergone organ, bone marrow, or peripheral blood stem cell transplantation, and those with acute myelogenous leukemia, lymphoma, diabetic ketoacidosis, nonketotic diabetes mellitus, amoebic colitis, typhoid fever, pellagra, kwashiorkor, malaria, malnutrition, meningococcaemia, and prematurity.[32,81] This type of mucormycosis has rarely occurred after renal, liver, and heart transplantation.[81] A bone marrow transplant patient with graft-versus-host disease developed *Mucor indicus* hepatic mucormycosis after consuming naturopathic medicine. *M. indicus* was a cure from the hepatic abscess and naturopathic medicine. Both were similar by arbitrary-primed polymerase chain reaction analysis reported by Oliver et al.[82] In infants and children, one-third of cases of gastrointestinal mucormycosis is taking place. Followed by the small intestine (24%) in children below one year of age, the stomach (59%) and colon (53%) have been the most commonly involved sites. In 2-18 years old children, the stomach has been involving in 85% of cases, oesophagus in 38% of cases, small bowel in 31% of cases, and colon in 31% of cases. In 50% of the cases, malnutrition has been present. [83] Generally, the prevalent segments involved are the stomach, followed by the large bowel.[84,85] In an ordinary host, intestinal mucormycosis is rare. After the nasogastric intubation and in the presence of known gastric ulcers developed gastric mucormycosis. When the

high risk of gastrointestinal perforation and exsanguination is occurring, then surgical intervention is usually necessary.[32]

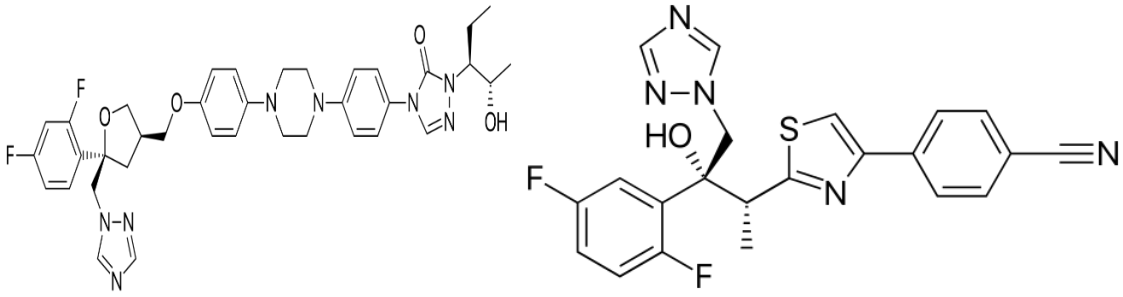
- **Miscellaneous:** Prosthetic valve endocarditis is rarely causing by mucormycosis.[32] An unusual case of Mucorales causing aortic thrombosis in a patient with the myelodysplastic syndrome was reported by Kalayjian et al. Hyphal invasion throughout the entire thickness of the aortic wall, with no organ involvement, was noted at autopsy.[86] In intravenous drug users, isolated renal mucormycosis has developed. The patients who have undergone renal transplantation in warmer climates and developing countries such as India, Egypt, Saudi Arabia, Kuwait, and Singapore have also happened.[87,88] After the traumatic inoculation or surgical intervention (i.e., tibial pin placement, anterior cruciate ligament repair) generally occurs Osteomyelitis.[89] Have reported osteomyelitis of the tibia, cuboid, calcaneus, humerus, femur, scapula, metacarpals, phalanges, and sternum. The bone infection of hematogenous osteomyelitis is rare.[90]

Diagnostic Methods: It includes cautions evaluation of clinical manifestations, Magnetic Resonance Imaging (MRI) modalities, use of Compound Tomography (CT) in the primitive stages, specialist valuation of cytological and histological provision, excellent application of clinical, microbiological technique, and execution of molecular detection.[6,37] For evaluation of patient's possibility, for invasive mucormycosis detection of host factors extensively. The various laboratory techniques for detecting mucor are PAS stains, direct examination, calcofluor, histopathological examination, gomori methenamine silver stain, culture, molecular methods, and fluorescent in situ hybridization.[37] According to Kontoyiannis et al., there is a need for a sensitive non-culture based investigative-based method is required because a major problem in the identification of mucormycosis includes its indefinable clinical appearance and recurrent occult distribution. The technique using for confirmation is the gold standard analytical technique is the tissue-based analysis.[6,38]

1. **Histopathology characteristics:** On test, the affected tissue with lesions show broad necrosis with numerous large branching pale-staining, wide, flat non-septal hyphae with branching at right or obtuse angles. In the culture media, are also frequently seen around or ovoid sporangia. Non - parallel sides of the thin-walled hyphae (infrequently septae) ranging from 3 to 25µm in diameter, branching irregularly and often with bulbous hyphal swelling. The signs of angio – invasion, and infarction might see in Necrotic tissue containing hyphae. The staining of choice is Gomori Methamine Silver (Grocott) or Periodic - acid Schiff.[6]
2. **Radiographic characteristics:** In conjunction with patchy effacement of the bony walls of the sinuses, opacification of the sinuses may observe. "Black turbinate sign" mentions an area of non-enhancing mucosa on the MRI interpreted cavernous sinus thrombophlebitis mucor infection.[57]
3. **Serology:** The antibody tests like Enzyme-Linked Immunosorbent Assays (ELISA), immunoblots, and immunodiffusion tests evaluate with variable success.[40,41,42,43] An Enzyme-Linked Immunospot (ELISpot) assay were detected Mucorales specific T cells in three hematological patients who developed invasive mucormycosis.[43,44]
4. **Molecular Assays:** It includes conventional Polymerase Chain Reaction (PCR), Restriction Fragment Length Polymorphism (RFLP) analyses, DNA sequencing of defined gene regions, and melt curve analysis of PCR products.[45,46,47,48,49,50,51] All above-mention assays can be used either for the detection or identification of Mucorales. The internal transcribed spacer or the 18S rRNA genes are either targeted by the majority of the molecular assays.[43] By using either formalin-fixed, paraffin-embedded, or fresh tissue samples yet resulting in different performance have done by the several studies. The sensitivity (70-100%) and specificity varied among the studies performed, with the best disadvantage being the low number of patients studied.[52] The molecular-based diagnosis from blood and serum has yielded promising clinical data directed by recent attempts.[43] In the earlier diagnosis, when compared to culture and overall confirmed culture-proven cases are results by molecular-based diagnosis from serum. Presently, in complement conventional diagnostic procedures, molecular-based diagnostic assays can be recommended as value add-on tools.[43,52,]
5. **Computed Tomography:** On the primary computed tomography (CT) scan, the most common radiological pattern of lung mucormycosis is a halo sign and then nodule or mass.[60,61] However, when studied very soon and on the serial follow-up, the sequential morphologic changes be detected as (i) reversed halo sign followed by (ii) consolidation or nodule or mass with halo sign and, finally, (iii) central necrosis and air-crescent sign. A recent study showed that in the pulmonary mucormycosis, there was a significant increase in the prevalence of reversed halo signs in neutropenic (79%) and non-neutropenic (31%) patients ($P < 0.05$).[58]
6. **Differential Diagnosis:** Maxillary sinus neoplasia, maxillary sinus aspergillosis, soft tissue infarction, soft tissue radionecrosis, other deep fungal infections included by the differential finding of mucormycosis.[39]

Treatment: A rapid, accurate diagnosis, surgical debridement, and administration of drugs with an adjunctive application of hyperbaric oxygen, recombinant cytokines, or transfusion of granulocyte and prosthetic obturator included as a successful treatment for mucormycosis.[6,53,54] Presently available

monotherapy shows a high mortality rate, especially with hematology patients, and hence proposed the choice of "Combination therapy" for mucormycosis, according to Spellberg et al.[53] Treat invasive mucormycosis and invasive aspergillosis; the drug isavuconazole recently approves by FDA. The fungal infection of mucormycosis is dangerous, and it needs to treat with prescription antifungal medicines such as amphotericin B, posaconazole, isavuconazole, and these medicines are given through vein amphotericin B (polyene), posaconazole (triazole), isavuconazole (triazole), or mouth (posaconazole, isavuconazole) shown in figure-5.



Posaconazole Isavuconazole

Figure-5: Medicines of mucormycosis.

The disease must observe for any symptoms of re-emergence. In some cases of this infection involving the nasal cavity and the brain, removal of infected brain tissue may require; hence, the surgical therapies were very drastic. In some cases sometimes involve the removal of the palate, nasal cavity, or eye structures; hence the surgery may be disfiguring in some cases. More than one operation may extend the surgery. The higher oxygen pressure increases the ability of neutrophils to kill the fungus; hence hyperbaric oxygen may be beneficial as an adjunctive therapy.[5,21,22]

- **Amphotericin B:** Amphotericin B therapy should instantly administer due to the rapid spread and high mortality rate of the diseases when mucormycosis is suspected. To ensure that eradication of the infection, amphotericin B is usually managed for an additional 4–6 weeks later begins the initial therapy. The surgical removal of the "fungus ball" is indicated after administration of either the amphotericin B (shown in figure-6) or posaconazole medicines.[5]

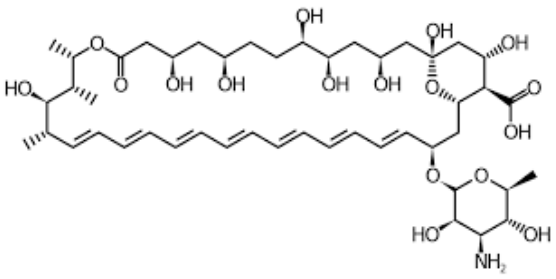


Figure-6: Structure of Amphotericin B.

The only antifungal drugs with in vitro activity against Mucorales are amphotericin B (Amb) and its lipid formulations and posaconazole.[66.67] Recently the antifungal armamentarium enlarged with the development of isavuconazole. Liposomal Amb (L-Amb) or Amb lipid complex (ABLC) is a first-line recommended antifungal agent.[68] The efficacy of liposomal amphotericin B (L-Amb) and amphotericin B lipid complex (ABLC) was dependent on the dose given, and that 10 mg/kg yielded the best outcomes proposed by studies in mice. The potency and tolerance of high-dose (10 mg/kg/day) L-Amb in association with surgery, when suggesting the treatment of 34 mucormycosis cases, are evaluated by a prospective French phase II multicenter study (AmBizygo trial). At week 12, a favorable response is seeing in 45% of patients. However, in 40% of patients, serum creatinine is doubled, but in 63% of cases, once the treatment had ended, creatinine levels normalized after three months.[69]

Figure-7: Liposomal Amphotericin B Injection.

The use of liposomal amphotericin B (L-Amb) (shown in figure-7) with a daily dosage of at least 5 mg/kg/day for mucormycosis recommended by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/ European Confederation of Medical Mycology (ECMM) and European Conference on Infections in Leukemia (ECIL-6) guidelines and dosages at 10 mg/kg/day strongly supported by ESCMID/ ECMM for cerebral infections.[68,70] Moreover, liposomal amphotericin B (L-Amb) should favor central nervous system infections because of better diffusion.[71]

Prognosis and Morbidity Rate: The prognosis usually depends on the extension of the disease, and an effective treatment starts a response to the infection. Without any systemic diseases, the survival rate for rhino-cerebral disease in patients is about 75%; with other disease is about 20%, and in pulmonary diseases is considered to be deadly. The rate of survival varies with foci of the infection: rhino cerebral mucormycosis – 45%, focal cerebral mucormycosis – 33%, pulmonary forms – 36%, sinusitis without cerebral participation – 87%, cutaneous isolated – 90%, disseminated disease – 16%, and involvement of gastrointestinal infection –10%.[44,45] The better rate of survival can achieve in patients with low baseline serum concentration of iron/ferritin, neutropenia, and malignant cases are not associated with infection.[6]

CONCLUSION

Mucormycosis is a life-threatening and highly invasive fungal infection, particularly affecting immunocompromised or diabetic patients. This infection is causing by the members of Mucorales and zygomycotic species and often affects the skin, sinuses, lungs, and brain. You can come into contact with the mold spores or can inhale them in things like soil, rotting produce or bread, or compost piles. The infection can happen to anybody at any age. Many peoples will come into contact with the fungus at some point in their everyday lives. Recently developed medications and treatments have several pathogeneses, but a cure for mucormycosis is still a challenge. Several medicines and treatments have slowed the mortality but still possess a challenge in curing Mucorales. There is no other way to avoid breathing in spores. But you can do a few things to decrease your chances of mucormycosis. It is particularly vital if you have a weak or ill-health condition that raises your risk. Stay away from the areas with a lot of dust or soil, like construction or excavation sites, traffic areas. Wear a surgical face mask or N95 face mask if you have to be in these areas. Avoid drinking and using the infected and polluted water. It can include floodwater or water-damaged buildings, particularly after natural disasters like hurricanes or floods. If you have weak immunity, avoid activities that involve dust and soil, like gardening or yard work. Wash cuts or scrapes, minor injuries with soap and water as soon as possible you can. If you get mucormycosis, be sure to take your medications as directed by the medical practitioner. If side effects cause problems or the infection doesn't get better and cure or any other health problem, let your doctor know right away without any hesitation.

REFERENCES

1. Kwon-Chung KJ; Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. Clinical Infectious Diseases, 2012; 54(suppl_1): S8-15.
2. Dr. G. Nishanth, Dr. N. Anitha, Dr. N. Arvindha Babu, Dr. L. Malathi; Europian Mucormycosis-A Review, Journal of Molecular and Clinical Medicine, 2020; 07(03): 1786.
3. James, William D, Berger, Timothy G; et al. Andrews' Diseases of the Skin: clinical Dermatology. Saunders Elsevier, 2006.
4. Rinaldi M.G.; "Zygomycosis". Infect Dis Clin North Am, 1989; 3(1): 19–41.
5. Dr. Dhrubo Jyoti Sen, Kushal Nandi, Dr. Beduin Mahanti, Dr. Dhananjoy Saha; Saprophytic Parasite and Mycosis by Black Fungus. Europian Journal of Pharmaceutical and Medical Research, 2021; 8(5): 742-746.
6. Ramalingam Suganya, Narasimhan Malathi, Vinithra Karthikeyan, Vyshnavi Devi Janagaraj; Mucormycosis: A Brief Review. Journal of Pure and Applied Microbiology, 2019; 13(1): 162.
7. Mohammadi R, Nazeri M, Sayedayn SM, Ehteram H; A successful treatment of rhinocerebral mucormycosis due to Rhizopus oryzae. Journal of research in medical sciences: The Official Journal of Isfahan University of Medical Sciences, 2014; 19(1): 72.
8. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP; Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clinical Infectious Diseases, 2005; 41(5): 634-53.
9. Bitar D, Van Cauteren D, Lanternier F; et al. Increasing incidence of zygomycosis (mucor-mycosis), France, 1997–2006. Emerg Infect Dis., 2009; 15: 1395–1401.
10. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP; Epidemiology and clinical manifestations of mucormycosis. Clinical Infectious Diseases, 2012; 54(suppl_1): S23-34.
11. Hibbett DS, Binder M, Bischoff JF; et al. A higher-level phylogenetic classification of the Fungi. Mycol Res., 2007; 111: 509–47.
12. Ashraf S. Ibrahim, Brad Spellberg, Thomas J. Walsh, Dimitrios P. Kontoyiannis; Pathogenesis of Mucormycosis, CID, 2012 Feb 1; 54(Suppl 1): S16.
13. Ribes JA, Vanover-Sams CL, Baker DJ; Zygomycetes in human disease. Clin Microbiol Rev., 2000; 13: 236–301.
14. Roden MM, Zaoutis TE, Buchanan WL; et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis., 2005; 41: 634–53.
15. Spellberg B, Edwards J Jr, Ibrahim A; Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev., 2005; 18: 556–69.
16. Sugar AM; Agents of mucormycosis and related species. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases. 6th ed. Philadelphia, PA: Elsevier, 2005: 2979.
17. Ibrahim AS, Edwards JE, Filler SG; Zygomycosis. In: Dismukes WE, Pappas PG, Sobel JD, eds.

Clinical mycology. New York, NY: Oxford University Press, 2003: 241–51.
18. Marr KA, Carter RA, Crippa F, Wald A, Corey L; Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis., 2002; 34: 909–17.
19. Waldorf AR, Ruderman N, Diamond RD; Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J. Clin. Invest., 1984; 74: 150 60.
20. Tedder M, Spratt JA, Anstadt MP, Hegde SS, Tedder SD, Lowe JE; Pulmonary mucormycosis: results of medical and surgical therapy. Ann. Thorac. Surg., 1994; 57(4): 1044- 50.
21. Koehler Philipp, Bassetti Matteo, Chakrabarti Arunaloke, Chen Sharon C A, Colombo Arnaldo Lopes, Hoenigl Martin, Klimko Nikolay, LassFlörl Cornelia, Oladele Rita O, Vinh Donald C, Zhu Li-Ping; "Defining and managing COVID-19-associated pulmonary aspergillosis: the, 2020. ECMM/ISHAM consensus criteria for research and clinical guidance". The Lancet Infectious Diseases.
22. Garg Deepak, Muthu Valliappan, Sehgal Inderpaul Singh, Ramachandran Raja, Kaur Harsimran, Bhalla Ashish, Puri Goverdhan D, Chakrabarti Arunaloke, Agarwal Ritesh; "Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature". Mycopathologia, 2021; 186(2): 289–298.
23. Garcia-Covarrubias L, Bartlett R, Barratt DM, Wassermann RJ; Rhino-orbitocerebral mucormycosis attributable to Apophysomyces elegans in an immunocompetent individual: case report and review of the literature. J. Trauma, 2001; 50: 353–357.
24. Lanternier F, Poiree S, Elie C, Bakouboula P, Ribaud P, Wolff M; et al. Pilot ProspectiveStudy of High Dose (10 mg/kg/d) Liposomal Amphotericin B (L-AmB) for the Initial Treatment of Zygomycosis: AMBIZYGO Trial 50th ICAAC, American Society for Microbiology, Boston, 2010 (Abstract M-1046).
25. Rees JR, Pinner RW, Hajjeh RA, Brandt ME, Reingold AL; The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992– 1993: results of population-based laboratory active surveillance. Clin. Infect. Dis., 1998; 27: 1138–1147.
26. Yamazaki T, Kume H, Murase S, Yamashita E, Arisawa M; Epidemiology of visceral mycoses: analysis of data in annual of the pathological autopsy cases in Japan. J. Clin. Microbiol., 1999; 37: 1732–1738.
27. Maertens J, Demuynck H, Verbeken EK; et al. Mucormycosis in allogeneic bone marrow transplant recipients:report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplant, 1999; 24: 307–312.
28. Marty FM, Cosimi LA, Baden LR; Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell trans-plants. N. Engl. J. Med., 2004; 350: 950–952.
29. Sugar AM; Agents of mucormycosis and related species. In: Mandell, GI, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 5th edn. New York: Churchill Livingstone, 2000; 2685–95.
30. Chakrabarti A, Kumar P, Padhye AA; et al. Primary cutaneous zygomycosis due to Saksenaea vasiformis and Apophysomyces elegans. Clin Infect Dis., 1997; 24: 580–3.
31. Espinel-Ingroff A, Oakley LA, Kerkering TM; Opportunistic zygomycotic infections. Mycopathologia, 1987; 97: 33–41.
32. R. M. Prabhu, R. Patel; Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect, 2004; 10(Suppl. 1): 31–47.
33. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston VI; Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis., 2000; 30: 851–6.
34. Lee FY, Mossad SB, Adal KA; Pulmonary mucormycosis: the last 30 years. Arch Intern Med., 1999; 159: 1301–9.
35. Funada H, Matsuda T; Pulmonary mucormycosis in a hematology ward. Intern Med, 1996; 35: 540–4.
36. Talmi YP, Goldschmeid-Reouven A, Bakon M; et al. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg, 2002; 127: 22.
37. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP; Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clinical Infectious Diseases, 2012; 54(suppl 1): S55-60.
38. Kontoyiannis DP, Lionakis MS, Lewis RE; et al. Zygomycoses in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J. Infect. Dis., 2005; 191: 1350–60.
39. Sciubba JJ, Regezi JA, Rogers RS; PDQ oral disease: diagnosis and treatment. PMPH-USA; 2002.
40. Sandven PER, Eduard W; Detection and quantitation of antibodies against Rhizopus by enzyme-linked immunosorbent assay. APMIS, 1992; 100: 981–987.
41. Wysong DR, Waldorf AR; Electrophoretic and immunoblot analyses of Rhizopus arrhizus antigens. J Clin Microbiol, 1987; 25: 358–363.
42. Jones KW, Kaufman L; Development and evaluation of an immunodiffusion test for diagnosis of systemic zygomycosis (mucormycosis): preliminary report. Clin Microbiol, 1978; 7: 97–101.
43. A. Skiada, C. Lass-Floerl, N. Klimko, A. Ibrahim, E. Roilides, G. Petrikkos; et al. Challenges in the diagnosis and treatment of mucormycosis; Medical Mycology, 2018; 56: S93–S101.

44. Potenza L, Vallerini D, Barozzi P; et al. Mucorales-specific T cells emerge in the course of invasive mucormycosis and may be used as a surrogate diagnostic marker in high-risk patients. Blood, 2011; 118: 5416–5419.
45. Hsiao CR, Huang L, Bouchara J-P, Barton R, Li HC, Chang TC; Identification of medically important molds by an oligonucleotide array. J Clin Microbiol, 2005; 43: 3760–3768.
46. Nagao K, Ota T, Tanikawa A; et al. Genetic identification and detection of human pathogenic Rhizopus species, a major mucormycosis agent, by multiplex PCR based on internal transcribed spacer region of rRNA gene. J Dermatol Sci., 2005; 39: 23–31.
47. Larche J, Machouart M, Burton K; et al. Diagnosis of cutaneous mu- ´ cormycosis due to Rhizopus microsporus by an innovative PCR-restriction fragment-length polymorphism method. Clin Infect Dis., 2005; 41: 1362– 1365.
48. Machouart M, Larche J, Burton K; et al. Genetic identification of the ´ main opportunistic mucorales by PCR-restriction fragment length polymorphism. J Clin Microbiol, 2006; 44: 805–810.
49. Nyilasi I, Papp T, Csernetics A, Krizs ´ an K, Nagy E, V ´ agv ´ olgyi C; High affinity iron permease (FTR1) gene sequence-based molecular identification of clinically important Zygomycetes. Clin Microbiol Infect, 2008; 14: 393–397.
50. Springer J, Lackner M, Ensinger C; et al. Clinical evaluation of a Mucorales-specific real-time PCR assay in tissue and serum samples. J Med Microbiol, 2016; 65: 1414–1421.
51. Kasai M, Harrington SM, Francesconi A; et al. Detection of a molecular biomarker for zygomycetes by quantitative PCR assays of plasma, bronchoalveolar lavage, and lung tissue in a rabbit model of experimental pulmonary zygomycosis. J Clin Microbiol, 2008; 46: 3690–3702.
52. Lackner M, Caramalho R, Lass-Florl C; Laboratory diagnosis of mucormycosis: current status and future perspectives. Future Microbiol, 2014; 9: 683–695.
53. Spellberg B, Ibrahim A, Rolides E, Lewis RE, Lortholary O, Petrikkos G, Kontoyiannis DP, Walsh TJ; Combination therapy for mucormycosis: why, what, and how? Clinical infectious diseases, 2012; 54(suppl 1): S73-8.
54. Sipsas N, Gamaletsou M, Anastasopoulou A, Kontoyiannis D; Therapy of mucormycosis. Journal of Fungi, 2018; 4(3): 90.
55. Petrikkos G, Skiada A, Sambatakou H; et al. Mucormycosis:ten-year experience at a tertiary-care center in Greece. Eur. J. Clin. Microbiol. Infect Dis., 2003; 22: 753–756.
56. Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O; Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. Ind. J. Ophthalmol., 2003; 51: 231–236.
57. Safder S, Carpenter JS, Roberts TD, Bailey N; The "black turbinate" sign: an early MR imaging finding of nasal mucormycosis. AJNR. Amer. J. Neuroradiol., 2010; 31: 771-774.
58. Bourcier J, Heudes PM, Morio F; et al.: Prevalence of the reversed halo sign in neutropenic patients compared with non-neutropenic patients: Data from a single-centre study involving 27 patients with pulmonary mucormycosis (2003-2016). Mycoses, 2017; 60(8): 526–33
59. Fürbringer, P. Beobachtungen über Lungenmycose beim Menschen. Virchows Arch., 1876; 66: 330–365.
60. Nam BD, Kim TJ, Lee KS; et al.: Pulmonary mucormycosis: serial morphologic changes on computed tomography correlate with clinical and pathologic findings. Eur Radiol, 2018; 28(2): 788–95.
61. Legouge C, Caillot D, Chrétien ML; et al.: The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia? Clin Infect Dis., 2014; 58(5): 672–8.
62. Marx RE, Stern D; editors. Inflammatory, Reactive and Infectious Diseases in Oral and Maxillofacial Pathology. Carol Stream III, USA: Quintessence Publishing, 2003; 104-6.
63. Kajs-Wyllie M; Hyperbaric oxygen therapy for rhinocerebral fungal infection. J Neurosci Nurs, 1995; 27: 174-81.
64. Mohindra S, Mohindra S, Gupta R, Bakshi J, Gupta SK; Rhinocerebral mucormycosis: The disease spectrum in 27 patients. Mycoses, 2007; 50: 290-6.
65. Bakathir AA; Mucormycosis of the jaw after dental extractions: Two case reports. Sultan Qaboos Univ Med J., 2006; 6: 77-82.
66. Sabatelli F, Patel R, Mann PA; et al.: In vitro activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. Antimicrob Agents Chemother, 2006; 50(6): 2009–15.
67. Amyroudis NG, Sutton DA, Fothergill AW; et al.: In vitro susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. Antimicrob Agents Chemother, 2007; 51(7): 2587–90.
68. Cornely OA, Arikan-Akdagli S, Dannaoui E; et al.: ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect, 2014; 20 Suppl 3: 5–26.
69. Lanternier F, Poiree S, Elie C; et al.: Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother, 2015; 70(11): 3116–23.
70. Tissot F, Agrawal S, Pagano L; et al.: ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica, 2017; 102(3): 433–44.

71. Lamoth F, Chung SJ, Damonti L; et al.: Changing Epidemiology of Invasive Mold Infections in Patients Receiving Azole Prophylaxis. Clin Infect Dis., 2017; 64(11): 1619–21.
72. Record NB, Ginder DR; Pulmonary phycomycosis without obvious predisposing factors. JAMA, 1976; 235: 1256-7.
73. Zeilender S, Drenning D, Glauser FL, Bechard D; Fatal Cunninghamella bertholletiae infection in an immunocompetent patient. Chest, 1990; 97: 1482–3.
74. Wall SJ, Lee KH, Alvarez JD, Bigelow DC; Quiz case 1. Cutaneous mucormycosis of the external ear. Arch Otolaryngol Head Neck Surg, 2000; 126: 238–9.
75. Wajszczuk CP, Dummer JS, Ho M, Van Thiel TE, Iwatsuki S, Shaw B; Fungal infections in liver transplant recipients. Transplantation, 1985; 40: 347–53.
76. Adam RD, Hunter G, DiTomasso J, Comerci G Jr; Mucormycosis: emerging prominence of cutaneous infections. Clin Infect Dis., 1994; 19: 67–76.
77. Nosari A, Oreste P, Montillo M; et al. Mucormycosis in hematologic malignancies: an emerging fungal infection. Haematologica, 2000; 85: 1068–71.
78. Nolan RL, Carter RR 3rd, Griffith JE, Chapman SW; Subacute disseminated mucormycosis in a diabetic male. Am J Med Sci., 1989; 298: 252–255.
79. Eucker J, Sezer O, Graf B, Possinger K; Mucormycoses. Mycoses, 2001; 44: 253–60.
80. Singh N, Gayowski T, Singh J, Yu VL; Invasive gastrointestinal zygomycosis in a liver transplant recipient: case report and review of zygomycosis in solid-organ transplant recipients. Clin Infect Dis., 1995; 20: 617–20.
81. Martinez EJ, Cancio MR, Sinnott J, Tt Vincent AL, Brantley SG; Nonfatal gastric mucormycosis in a renal transplant recipient. South Med J., 1997; 90: 341–4.
82. Oliver MR, Van Voorhis WC, Boeckh M, Mattson D, Bowden RA; Hepatic mucormycosis in a bone marrow transplant recipient who ingested naturopathic medicine. Clin Infect Dis., 1996; 22: 521–4.
83. Michalak DM, Cooney DR, Rhodes KH, Telander RL, Kleinberg F; Gastrointestinal mucormycosis in infants and children: a cause of gangrenous intestinal cellulitis and perforation. J Pediatr Surg., 1980; 15: 320–4.
84. Parfrey NA; Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. Medicine, 1986; 65: 113–23.
85. Lehrer RI, Howard DH; et al. Mucormycosis. Ann Intern Med, 1980; 9: 93–108.
86. Kalayjian RC, Herzig RH, Cohen AM, Hutton MC; Thrombosis of the aorta caused by mucormycosis. South Med J., 1988; 81: 1180–2.
87. Stas KJ, Louwagie PG, Van Damme BJ, Coosemans W, Waer M, Vanrenterghem YF; Isolated zygomycosis in a bought living unrelated kidney transplant. Transpl Int., 1996; 9: 600–2.
88. Weng DE, Wilson WH, Little R, Walsh TJ; Successful medical management of isolated renal zygomycosis: case report and review. Clin Infect Dis., 1998; 26: 601–605.
89. Burke WV, Zych GA; Fungal infection following replacement of the anterior cruciate ligament: A case report. J Bone Joint Surg Am, 2002; 84A: 449–53.
90. Echols RM, Selinger DS, Hallowell C, Goodwin JS, Duncan MH, Cushing AH; Rhizopus osteomyelitis. A case report and review. Am J Med, 1979; 66: 141–5