International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1303-1312 www.ijprajournal.com ISSN: 2249-7781

A Review: Mucormycosis (Black Fungus)

Sneha B Sable*,Aditi D Sadgir ,Kalyani S Mhaismale and Pallavi L Phalke
MatoshriRadha College of Pharmacy, Virgav Akole.

Submitted: 10-05-2023 Accepted: 23-05-2023

ABSTRACT- Mucormycosis is a new angioinvasive infection caused by the ubiquitous filamentous fungus of the mucorales order order of the zygomycete class. It is a rare disease but increasingly recognized in immune compromised patients. It can be categorized into
Pulmonary, Rhinocerebral, Cutaneous, Gastrointestinal and Disseminated types.Black fungus is an opportunistic pathogen that affects immune compromised patients due to comorbidities, excessive administration of steroids, organ transplantation, exposure to ventilation, oxygen therapy, poor hospital hygiene, etc
KEYWORDS-Mucormycosis,Black Fungus,Pathophysiology,Types,diagnosis and Testing,Treatement

I. INTRODUCTION

Black fungus, also referred to as mucormycosis, is a rare but serious condition. It is brought on by a class of moulds called mucormycetes and frequently impacts the sinuses, lungs, skin, and brain. Inhaling the mould spores or coming into contact with them through items like dirt, stale bread or vegetables, compost piles, or other objects are both possible ways to contract the disease.

Mucormycetes are a group of moulds that produce the lethal but uncommon fungal infection known as mucormycosis (formerly called zygomycosis). These moulds are present everywhere in the environment. People with medical conditions or those who take medications that impair the body's natural defences against disease and infection are more likely to develop mucormycosis. After breathing in fungus spores from the air, it typically affects the sinuses or the lungs. After a burn, cut, or another kind of physical trauma, it may also manifest itself on the skin.

HISTORY

The first instance of mucormycosis may have been reported by Friedrich Küchenmeister in 1855[1].Fürbringer provided the first account of the lung disease in 1876.[2] Lichtheim not only described how the illness first appeared in rabbits in 1884 but also distinguished between two different species, Mucor corymbifera and Mucor rhizopodiformis. Later, these two species were known as Lichtheimia and Rhizopus, respectively.[1]

A link between poorly controlled diabetes and severe sinus, brain, and ocular involvement has been discovered in three patients from 1943 [1].

Saksenaea vasiformis was identified as the root cause of numerous cases when it was found in soil from an Indian jungle in 1953. When P. C. Misra examined soil from an Indian mango plantation in 1979, he found Apophysomyces; this bacterium was later found to be the main culprit behind mucormycosis.Since then, a number of additional species have been added to the mucorales.[1] When cases were initially reported in the United States in the middle of the 1950s, the author thought that the use of antibiotics, ACTH, and steroids was to blame.[2][3]. Up until the second part of the 20th century, the only medication on the market was potassium iodide. A review of instances from 1970 to 2000 where the diagnosis was made through flexible bronchoscopy.

Patients who underwent both surgical and medical treatment, particularly when given amphotericin B[2], fared better in terms of survival.

Arnold Paltauf coined the term "mycosis mucorina" after describing a case with systemic symptoms affecting the sinuses, brain, and gastrointestinal tract in 1885. As a result, "mucormycosis" gained more notoriety.[1] Despite the fact that the term "mucormycosis" has been dropped due to changes in the taxonomy of the kingdom Fungi, the terms "zygomycosis" and "mucormycosis" are frequently used interchangeably.

Entomophthorales is one of the Mucorales of the extinct phylum Zygomycota. Diseases caused by fungus in the order Mucorales are referred to as "mucormycosis".[4]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1303-1312 www.ijprajournal.com ISSN: 2249-7781

MECHANISM OF MUCORMYCOSIS

After spores have formed, neutrophils are essential for removing fungal hyphae.

The host's defence mechanisms against the fungi that cause mucormycosis also involve macrophages and monocytes; in particular, alveolar macrophages stop spore germination[6].

Mucormycosis primarily affects immunosuppressed people because they lack these defence mechanisms.

Patients with diabetes and DKA are more likely to develop mucormycosis due to hyperglycemia, acidosis, and corticosteroid medication (more specifically, the phagocytic cell activities).[5]

Mucormycosis agents need to enter the host's vasculature in order to disseminate, get enough iron for growth from the host, and avoid the host's phagocytic defences.

The breakdown of proteins protecting iron in immunocompromised hosts (including diabetics) makes it available to fungi for growth inside the body.[7]

Transferrin's ability to bind iron is impaired by acidosis, most likely due to the displacement of ferric iron from transferrin by proton-mediated oxidation[8]. The ability to bind iron is reduced under acidotic circumstances.

Fungi can extract iron from their host in two different ways: using siderophores, which are low-molecular-weight iron chelators, or using high-affinity iron permeases.[9]

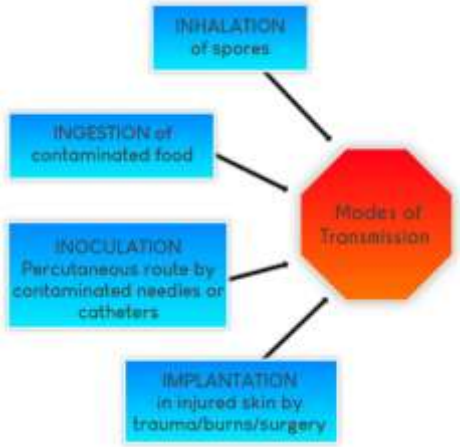
This mechanism causes a decrease in the number of neutrophils and phagocytes as well as the growth of fungi[10].

The fungus that causes mucormycosis damages endothelial cells, which results in vascular invasion, further dispersion, and tissue necrosis.

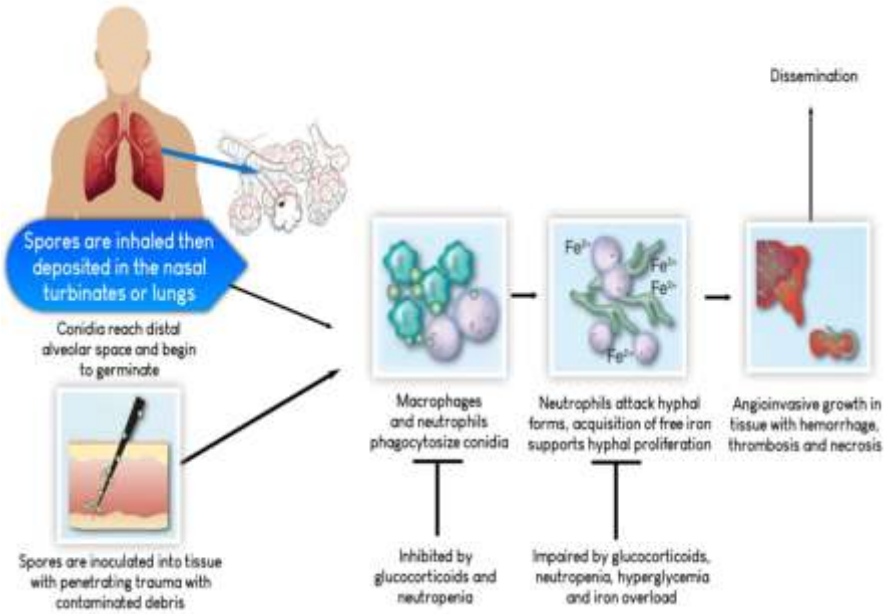
Laminin and type IV collagen found in the subendothelial matrix can attach to pregerminated R. oryzae spores but not germlings.[11][12]

The entry of Mucorales into endothelial cells is facilitated by the receptor glucose-regulated protein 78 (GRP78).

Endothelial cells are invaded and destroyed through receptor-mediated processes when iron and glucose levels are elevated.[13] These conditions are similar to those in diabetic ketoacidosis. These findings probably explain why diabetic ketoacidosis is more prone to mucormycosis than other types of ketoacidosis.



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1303-1312 www.ijprajournal.com ISSN: 2249-7781



COVID-19–ASSOCIATED MUCORMYCOSIS
AS OF JUNE 2021, COVID-ASSOCIATED MUCORYCOSIS HAS BEEN DETECTED IN THE COUNTRIES OF INDIA

More than 11,700 persons were undergoing treatment for mucormycosis during the COVID-19 pandemic in India, according to a May 25, 2021, report from the Indian government. Due to the fungus' ability to produce black-looking dead and rotting tissue, it was widely referred to as "black fungus" in Indian media. Mucormycosis rates in India were believed to be over 70 times higher than those in the rest of the world even before the COVID-19 epidemic.[14][15]

It has been labelled an epidemic by some state governments in India.[16] because of the epidemic-like increase in instances. One of the treatments needed daily injections over the course of eight weeks using the anti-fungal intravenous injectable known as amphotericin B, which was in low supply. You can deliver amphotericin B deoxycholate in either its regular form or a liposomal form. The liposomal variant was considered to be "safer, more effective, and [with] lesser side effects"[17] while being more expensive.The greatest obstacle to using antifungal drugs on black fungus is the paucity of clinical data. [18]

PATHOPHYSIOLOGY

Agents in Pathogenesis

In both developing and developed nations, immunocompromised hosts (such as transplant recipients, diabetics, leukopenic patients, acidotic patients, and dialysis patients who receive deferoxamine, an iron chelator) are susceptible to the potentially fatal fungal infection known as mucormycosis.[19][20][21][22][23]. Species from the family Mucoraceae are frequently isolated from mucormycosis patients.

Rhizopus oryzae (Rhizopus arrhizus) is the most prevalent cause of infection in the Mucoraceae. Cunninghamella spp. infection has also been linked to an increase in mucormycosis cases.

Transmission

The skin is a crucial barrier against the fungi that cause mucormycosis. Agents that cause mucormycosis typically cannot penetrate healthy skin.

However, the organism has the capacity to transmit disease by implanting itself in contaminated soil or water, producing burns, severe skin rashes, long-lasting skin maceration, and penetrating deeper tissues.

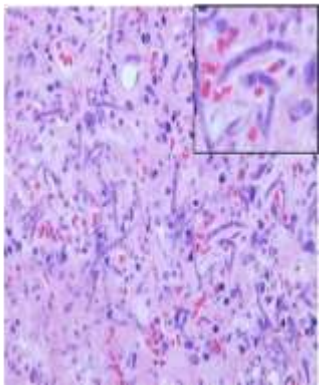
Furthermore, it has been established that contaminated surgical dressings and nonsterile adhesive tape are the main contributors to primary cutaneous mucormycosis. Transmission of gastrointestinal mucormycosis occurs through ingestion.

Breathing in Mucorales sporangiospores causes pulmonary mucormycosis in people with weakened immune systems, which develops into hematogenous spread. extensive pathology

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1303-1312 www.ijprajournal.com ISSN: 2249-7781

The lesions that develop in rhinocerebral or cutaneous mucormycosis can range in size from elevated red nodules or plaques that sporadically release purulent material to ulcerated lesions with central cavitation, red leaky cores, and raised epidermal edges.
Older lesions may have thicker, more erratic epidermis that completely or partially conceals them. Eschar that is dark in colour and suggests the possibility of necrosis and ischemia.[24]

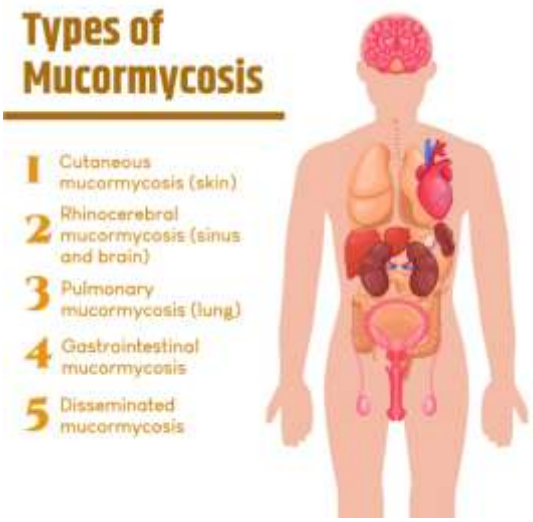
Microscopic Pathology
• Histologically analysed skin biopsies revealed discrete, poorly encapsulated granulomas, or more commonly
• Ribbon-like, thin-walled, non-pigmented, wide (5–20 m), pauciseptate hyphae with right-angle branching; • Thick-walled spherical forms can form at the hyphal extremities in lesions that are exposed to the air.[25]



TYPES OF MUCORMYCOSIS

A rare but fatal fungal infection known as mucormycosis, sometimes known as zygomycosis, is brought on by a group of moulds known as the mucormycetes. These fungi are present everywhere in the environment. They are present in compost piles, rotting wood, and other organic waste that is decomposing in soil.[26]

When fungal spores from the environment come in contact with people, mucormycosis results. For example, breathing in spores might result in sinus or lung infections. These kinds of mucormycosis frequently affect people with health issues or those who take medications that reduce the body's capacity to fight infection and disease.[27][28]



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1303-1312 www.ijprajournal.com ISSN: 2249-7781

MUCORMYCOSIS TYPES

A sinus infection called rhinocerebral (sinus and brain) mucormycosis has the potential to move to the brain. People with uncontrolled diabetes and kidney transplant recipients experience this more frequently.[29][30]

The most prevalent form of mucormycosis in cancer patients, transplant recipients, and stem cell recipients is pulmonary (lung) mucormycosis.

Infants and young children are more frequently affected by intestinal mucormycosis than are adults. If a newborn under one month old underwent surgery, received antibiotics, or underwent other immune-suppressing therapies, they may be at risk.[31][32]

A skin break allows the fungus to enter the body, causing cutaneous mucormycosis, a skin illness.

Following a burn, scrape, cut, surgery, or other type of skin trauma, this infection may manifest itself. When the immune system is working regularly, mucormycosis of the type that is most common develops.

The medical word for an illness that spreads to another section of the body via the bloodstream is diffuse mucormycosis. Although the infection primarily harms the brain, it can also affect the spleen, heart, and skin.

THE MOST TYPICAL FUNGUS THAT CAUSE MUCORMYCOSIS

Examples include Apophysomyces, Mucor, Rhizomucor, Syncephalastrum, Cunninghamella bertholletiae, Rhizopus, and Lichtheimia (formerly Absidia).[33]

SYMPTOMS OF MUCORMYCOSIS

Depending on where in the body the fungus is developing, mucormycosis symptoms change.[34][35][36][37] If you experience symptoms that you believe may be related to mucormycosis, consult your healthcare professional.

Mucormycosis of the nose and brain symptoms include:• rapid-escalating black lesions on the bridge of the nose or on the roof of the mouth; an edoema on one side of the face; sinusitis or nasal congestion; fever

Pulmonary (lung) mucormycosis symptoms and signs include:

Flu and cough
• Chest discomfort • Breathing issues

Blisters or ulcers may form as a result of cutaneous (skin) mucormycosis, and the affected region may turn black. Aching, warmth, severe redness, or swelling near to a wound are other symptoms.

Gastrointestinal mucormycosis symptoms and signs include:

• Internal bleeding; nausea and diarrhoea; constipation

It may be challenging to identify which symptoms are caused by dispersed mucormycosis given that the disease frequently affects patients who are already ill from other medical issues. Patients may lose their mental function or slip into a coma as a result of a spreading infection in the brain.

DIAGNOSIS AND TESTING

When diagnosing mucormycosis, doctors take into account your medical history, symptoms, physical examinations, and laboratory tests. A sample of fluid from your respiratory system may be taken by medical professionals who believe you have mucormycosis in your sinuses or lungs and sent to a lab for testing. Your doctor may do a tissue biopsy to look for signs of mucormycosis. During this procedure, a small sample of the diseased tissue is examined under a microscope or in a fungal culture in a laboratory. Depending on where the infection is thought to be, you could also require imaging tests, such as a CT scan of your lungs, sinuses, or other parts of your body.

TREATMENTFOR MOCORMYCOSIS

MEDICAL. For the best medical outcome, underlying systemic abnormalities such acidemia and hyperglycemia must be treated as soon as is practicable. Quick antifungal therapy is also required, as well as vigorous surgical intervention.

Amphotericin B, a lipid-based medication that breaks down the fungus' cell wall and should be given as soon as the diagnosis is made, is the first-line treatment for mucormycosis. When high doses are required, nephrotoxicity may happen, but liposomal formulations can provide high amounts while keeping renal function.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1303-1312 www.ijprajournal.com ISSN: 2249-7781

For mucormycosis, posaconazole has been recommended as an effective adjuvant or alternative therapy. The triazole stops the fungus from growing.[38][39][40][41] To completely understand posaconazole's role in the initial treatment of mucormycosis, more research is necessary.

As a result, it is not recommended to utilise it as a first-line therapy at this time.
Surgery should be taken into consideration early on in the course of treatment because systemic drugs frequently cannot reach the afflicted tissue due to vaso-occlusion.

SURGICAL. Early, aggressive surgical debridement is necessary for treating invasive fungal illness effectively. This can be done using either an open technique or an endoscopic technique. It is necessary to remove all necrotic tissue. The surgeon should keep removing tissue until normal, well-perfused bleeding tissue is discovered because bleeding from damaged tissues is uncommon. Daily repeat debridement may be required until clinical improvement is seen. When the disease has significantly advanced, sinus excision and orbital exenteration may be necessary.

There are four major strategies to treat mucormycosis: early detection, removing risk factors, quick antifungal therapy coupled with surgical excision of all affected tissues, and adjuvant medications.[42] Early detection is suspect in 50% of cases due to the restricted tools available, and is only diagnosed after post-mortem.[43] Only cutaneous and rhino-cerebral infections can be diagnosed using imaging tests and nasal endoscopy.[44] Million et al. reported utilising a polymerase chain reaction (PCR) method to locate mucorales DNA in blood samples three days before the discovery of Mucormycosis.[45]The patient needs imaging testing and a nasal endoscopy to check for mucormycosis if a Covid 19 patient with diabetes complains of headache and vision problems. Early discovery in this situation could prevent mortality because the fungus could eventually pierce the skull and cause death.

A mucormycosis sickness must be effectively treated by removing or controlling all predisposing factors. Since diabetes and ketoacidosis are the two conditions that Indian patients experience the most frequently, reducing blood sugar and managing ketoacidosis may stop mucorales from invading host tissues.[46] According to a study, using insulin and sodium bicarbonate together may help treat diabetic ketoacidosis.[47] When immunosuppressive drugs, especially steroids and deferoxamine, are taken sparingly or not at all, mucorales cannot infiltrate host tissues.[48]

If at all possible, the excision of the afflicted tissues is the best treatment option for mucormycosis. While some conditions, like a cutaneous or rhino-cerebral infection, make this easier, others, like lung disease or when a virus has infected the brain, make it impossible to do so.[49]According to a study, an early surgical excision of the infected sinuses in rhino-cerebral mucormycosis stops the illness from spreading to the eyes and results in higher cure rates of 85%. A study found that using antifungal medications during surgery reduced mortality from 70% to 14%.[50]

Several studies on the treatment of mucormycosis infection have found that the best antifungal drug is amphotericin B. Due to its low toxicity and superior CNS penetration, liposomal amphotericin B is frequently used at doses ranging from 5 mg/g/day to 10 mg/kg/day to treat patients with brain infections.[51][52] The doctor's assessment of the patient's underlying illness determined the length of the Amphotericin B treatment, which is still not correctly recorded. Amphotericin B should reportedly be administered for at least three weeks. Additional treatment options might include triazoles like posaconazole, isavuconazole, and voriconazole, among others, if radiological and clinical improvements are observed.[53]

Studies show that posaconazole has supplanted amphotericin B as the drug of choice for treating mucormycosis infection.[54] Posaconazole is more effective than itraconazole and less effective than amphotericin B, according to clinical investigations in animal models. Posaconazole is now more bioavailable when administered intravenously or as tablets. 48 The broad range triazole itraconazole has not been able to demotivate micorales in human clinical trials despite having strong anti-micorales action in vitro. In an in-vitro model, voriconazole failed to demonstrate efficacy against mucorales.[55][56][57] Triazoles shouldn't be used as the first line of treatment for mucormycosis because of this.

Capsofungin alone has minimal impact when tested in-vitro against mucorales in a mouse model of experimentation, however it exhibits

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1303-1312 www.ijprajournal.com ISSN: 2249-7781

synergistic effects when paired with amphotericin B. It barely ever causes any harm. Casofungin was found to be effective at inhibiting the (1-3)-D-glucan synthase enzyme generated by Rhizopus oryzae in an in vitro activity at low concentrations.[58]Other iron chelators, in addition to deferoxamine, are used as adjunctive therapy [59]. Iron chelators inhibited the fungus from absorbing iron and stopped its growth, in contrast to deferoxamine, which promotes mould growth.[60] By enhancing neutrophils' ability to combat mould, hyperbaric oxygen therapy also prevents the growth of the Mucormycosis mould.[61]

II. CONCLUSION

The air and surroundings both contain the fungi that cause the famed black fungus disease. It is therefore impossible to avoid them. Only those with insufficient protection or those who have just recovered from COVID-19 are vulnerable to this virus.

REFERENCES

[1]. Chander J (2018). "26. Mucormycosis". Textbook of Medical Mycology (4th ed.). New Delhi: Jaypee Brothers Medical Publishers Ltd. pp. 534–596. ISBN 978-93-86261-83-0.

[2]. Yamin HS, Alastal AY, Bakri I (January 2017). "Pulmonary Mucormycosis Over 130 Years: A Case Report and Literature Review". Turkish Thoracic Journal. **18** (1): 1–5.doi:10.5152/TurkThoracJ.2017.16033. PMC 5783164. PMID 29404149.

[3]. Baker RD (March 1957). "Mucormycosis; a new disease?". Journal of the American Medical Association. **163** (10): 805–8. doi:10.1001/jama.1957.02970450007003. PMID 13405736.

[4]. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, et al. (December 2019). "Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium". The Lancet. Infectious Diseases

[5]. Waldorf AR (1989). "Pulmonary defense mechanisms against opportunistic fungal pathogens". Immunol. Ser. 47: 243–71. PMID 2490078.

[6]. Spellberg B, Edwards J, Ibrahim A (2005). "Novel perspectives on mucormycosis: pathophysiology, presentation, and management". Clin. Microbiol. Rev. **18** (3): 556–69. doi:10.1128/CMR.18

[7]. Artis WM, Fountain JA, Delcher HK, Jones HE (1982). "A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability". Diabetes. **31** (12): 1109–14. PMID 6816646.

[8]. ↑ Ibrahim AS, Spellberg B, Edwards J (2008). "Iron acquisition: a novel perspective on mucormycosis pathogenesis and treatment". Curr. Opin. Infect. Dis. **21** (6): 620–5. doi:10.1097/QCO.0b013e3283165fd1. PMC 2773686. PMID 18978530.

[9]. ↑ Howard DH (1999). "Acquisition, transport, and storage of iron by pathogenic fungi". Clin. Microbiol. Rev. **12** (3): 394–404. PMC 100245. PMID 10398672.

[10]. ↑ Boelaert JR, de Locht M, Van Cutsem J, Kerrels V, Cantinieaux B, Verdonck A, Van Landuyt HW, Schneider YJ (1993). "Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies". J. Clin. Invest. **91** (5): 1979–86. doi:10.1172/JCI116419. PMC 288195. PMID 8486769.

[11]. ↑ Bouchara JP, Oumeziane NA, Lissitzky JC, Larcher G, Tronchin G, Chabasse D (1996). "Attachment of spores of the human pathogenic fungus Rhizopus oryzae to extracellular matrix components". Eur. J. Cell Biol. **70** (1): 76–83. PMID 8738422.

[12]. ↑ Ibrahim AS, Spellberg B, Avanessian V, Fu Y, Edwards JE (2005). "Rhizopus oryzae adheres to, is phagocytosed by, and damages endothelial cells in vitro". Infect. Immun. **73** (2): 778–83. doi:10.1128/IAI.73.2.778-783.2005. PMC 547117. PMID 15664916.

[13]. ↑ Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, Edwards JE, Filler SG, Ibrahim AS (2010). "The endothelial cell receptor GRP78 is required for

mucormycosis pathogenesis in diabetic mice". J. Clin. Invest. **120** (6): 1914–24. doi:10.1172/JCI42164. PMC 2877958. PMID 20484814.

[14]. Dyer O (May 2021). "Covid-19: India sees record deaths as "black fungus" spreads fear". BMJ. **373**: n1238. doi:10.1136/bmj.n1238. PMID 33985993.

[15]. Schwartz I, Chakrabarti A (June 2, 2021). "'Black fungus' is creating a whole other health emergency for Covid-stricken India". The Guardian. Retrieved June 3, 2021.

[16]. Wadhawan DW, Jain P, Shrivastava S, Kunal K (May 19, 2021). "Rajasthan declares black fungus an epidemic; cases pile up in several states | 10 points". India Today. Retrieved May 20, 2021.

[17]. "Black fungus in India: Concern over drug shortage as cases rise". BBC News. May 19, 2021. Retrieved July 8, 2021.

[18]. Spellberg B, Edwards J, Ibrahim A (July 2005). "Novel perspectives on mucormycosis: pathophysiology, presentation, and management". Clinical Microbiology Reviews. **18** (3): 556–69. doi:10.1128/cmr.18.3.556-569.2005. PMC 1195964. PMID 16020690.

[19]. Boelaert JR, Fenves AZ, Coburn JW (1991). "Deferoxamine therapy and mucormycosis in dialysis patients: report of an international registry". Am. J. Kidney Dis. 18 (6): 660–7. PMID 1962650.

[20]. Boelaert JR, Fenves AZ, Coburn JW (1989). "Registry on mucormycosis in dialysis patients". J. Infect. Dis. 160 (5): 914. PMID 2809271.

[21]. Ribes JA, Vanover-Sams CL, Baker DJ (2000). "Zygomycetes in human disease". Clin. Microbiol. Rev. 13 (2): 236–301. PMC 100153. PMID 10756000.

[22]. Spellberg B, Edwards J, Ibrahim A (2005). "Novel perspectives on mucormycosis: pathophysiology, presentation, and management". Clin. Microbiol. Rev. 18 (3): 556–69. doi:10.1128/CMR.18.3.556-569.2005. PMC 1195964. PMID 16020690.

[23]. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ (2005). "Epidemiology and outcome of zygomycosis: a review of 929 reported cases". Clin. Infect. Dis. 41 (5): 634–53. doi:10.1086/432579. PMID 16080086.

[24]. Connolly JH, Canfield PJ, Obendorf DL (2000). "Gross, histological and immunohistochemical features of mucormycosis in the platypus". J. Comp. Pathol. 123 (1): 36–46. doi:10.1053/jcpa.2000.0384. PMID 10906254.

[25]. Guarner J, Brandt ME (2011). "Histopathologic diagnosis of fungal infections in the 21st century". Clin. Microbiol. Rev. 24 (2): 247–80. doi:10.1128/CMR.00053-10. PMC 3122495. PMID 21482725.

[26]. Richardson M. The ecology of the Zygomycetes and its impact on environmental exposureexternal icon. 2009 Oct;15 Suppl 5:2-9.

[27]. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosisexternal icon. Clin Infect Dis. 2012 Feb;54 Suppl 1:S23-34.

[28]. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human diseaseexternal icon. Clin Microbiol Rev 2000; 13:236-301.

[29]. Song Y, Qiao J, Giovanni G, Liu G, Yang H, Wu J, Chen J. Mucormycosis in renal transplant recipients: review of 174 reported casesexternal icon. BMC Infect Dis. 2017 Apr; 17(1): 283.

[30]. Abdalla A, Adelmann D, Fahal A, Verbrugh H, Van Belkum A, De Hoog S. Environmental occurrence of Madurella mycetomatis, the major agent of human eumycetoma in Sudanexternal icon. J Clin Microbiol. 2002 Mar; 40(3): 1031–1036.

[31]. Vallabhaneni S, Mody RK. Gastrointestinal mucormycosis in neonates: a reviewexternal icon. Current Fungal Infect Rep. 2015.

[32]. Francis JR, Villanueva P, Bryant P, Blyth CC. Mucormycosis in children: review and recommendations for managementexternal icon. J Pediatric Infect Dis Soc. 2018 May 15;7(2):159-164.

[33]. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported casesexternal icon. Clin Infect Dis. 2005 Sep 1;41(5):634-53.

[34]. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosisexternal icon. Clin Infect Dis. 2012 Feb;54 Suppl 1:S23-34.

[35]. Lewis RE, Kontoyiannis DP. Epidemiology and treatment of mucormycosisexternal icon. Future Microbiol. 2013 Sep;8(9):1163-75.

[36]. Spellberg B, Edwards Jr. J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and managementexternal icon. Clin Microbiol Rev. 2005 Jul;18(3):556-69.

[37]. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human diseaseexternal icon. Clin Microbiol Rev 2000; 13:236-301.

[38]. Gamaletsou MN et al. Curr Infect Dis Rep. 2012;14(4):423-434

[39]. Thurtell MJ et al. Clin Experiment Ophthalmol. 2013;41(6):567-576.

[40]. Safder S et al. AJNR Am J Neuroradiol. 2010;31(4):771-774.

[41]. Vehreschild JJ et al. Crit Rev Microbiol. 2013;39(3):310-324.

[42]. S. Nithyanandam, M.S. Jacob, R.R. Battu, R.K. Thomas, M.A. Correa, O. D'Souza

[43]. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes

[44]. Indian J Ophthalmol, 51 (2003), pp. 231-236

[45]. T. Mori, M. Egashira, N. Kawamata, et al.Zygomycosis: two case reports and review of reported cases in the literature in JapanNihon Ishinkin Gakkai Zasshi, 44 (2003), pp. 163-179, 10.3314/jjmm.44.163

[46]. B.S. Khor, M.H. Lee, H.S. Leu, J.W. LiuR hinocerebral mucormycosis in Taiwan J Microbiol Immunol Infect, 36 (2003), pp. 266-269

[47]. L. Millon, F. LaRosa, Q. Lepiller, et al.Quantitative polymerase chain reaction detection of circulating DNA in serum for early diagnosis of mucormycosis in immunocompromised patientsClin. Infect. Dis, 56 (2013), pp. e95-e101, 10.1093/cid/cit094

[48]. B. Spellberg, J. Edwards Jr., A. Ibrahim Novel perspectives on mucormycosis: pathophysiology, presentation, and management Clin Microbiol Rev, 18 (3) (2005), pp. 556-569, 10.1128/CMR.18.3.556-569.2005

[49]. T. Gebremariam, L. Lin, M. Liu, et al. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis J Clin Invest, 126 (2016), pp. 2280-2294, 10.1172/JCI82744

[50]. J.A. Ribes, C.L. Vanover-Sams, D.J. Baker Zygomycetes in human disease Clin Microbiol Rev, 13 (2000), pp. 236-301, 10.1128/CMR.13.2.236

[51]. L. Millon, R. Herbrecht, F. Grenouillet, et al. Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF) Clin Microbiol Infect, 22 (9) (2016), pp. 810.E1-810.E8

[52]. S. Nithyanandam, M.S. Jacob, R.R. Battu, R.K. Thomas, M.A. Correa, O. D'Souza Rhino-orbito cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes Indian J Ophthalmol, 51 (2003), pp. 231-236

[53]. M.A. Barron, M. Lay, N.E. Madinger Surgery and treatment with high-dose liposomal amphotericin B for eradication of craniofacial zygomycosis in a patient with Hodgkin's disease who had undergone allogeneic hematopoietic stem cell transplantation J Clin Microbiol, 43 (2005), pp. 2012-2014, 10.1128/JCM.43.4.2012-2014.2005

[54]. A.A. Cagatay, S.S. Oncu, S.S. Calangu, T. T. Yildirmak, H.H. Ozsut, H.H. Eraksoy Rhinocerebral mcormycosis treated with 32 gram liposomal amphotericin B and incomplete surgery: a case reportBMC Infect Dis, 1 (2001), p. 22, 10.1186/1471-2334-1-22

[55]. D.P. Kontoyiannis, R.E. Lewis How I treat mucormycosis Blood, 118 (5) (2011), pp. 1216-1224, 10.1182/blood-2011-03-316430

[56]. O.A. Cornely, I.A. Alastruey, D. Arenz, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium Lancet Infect. Dis, 19 (2019), pp. e405-e421

[57]. E. Bouza, P. Munoz, J. Guinea Mucormycosis: an emerging disease? Clin Microbiol Infect, 12 (suppl 7) (2006), pp. 7-23, 10.1111/j.1469-0691.2006.01604.x

[58]. E. Dannaoui, J.F. Meis, D. Loebenberg, P. E. Verweij Activity of posaconazole in treatment of experimental disseminated zygomycosis Antimicrob Agents Chemother, 47 (2003), pp. 3647-3650, 10.1128/AAC.47.11.3647-3650.2003

[59]. M.A. Pfaller, S.A. Messer, R.J. Hollis, R. N. Jones Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program Antimicrob Agents Chemother, 46 (2002), pp. 1032-1037, 10.1128/AAC.46.4.1032-1037.2002 2000

[60]. B. Spellberg, Y. Fu, J.E. Edwards Jr., A.S. Ibrahim Combination therapy with amphotericin B lipid complex and caspofungin acetate of disseminated zygomycosis in diabetic ketoacidotic mice Antimicrob Agents Chemother, 49 (2005), pp. 830-832, 10.1128/AAC.49.2.830 832.2005

[61]. A.S. Ibrahim, J.C. Bowman, V. Avanessian, et al. Caspofungin inhibits Rhizopus oryzae 1,3-beta-D-glucan synthase, lowers burden in brain measured by quantitative PCR, and improves survival at a low but not a high dose during murine disseminated zygomycosis Antimicrob Agents Chemother, 49 (2005), pp. 721-727, 10.1128/AAC.49.2.721-727.2005

[62]. J.R. Boelaert, J.V. Cutsem, D.M. Locht, Y .J. Schneider, R.R. Crichton Deferoxamine augments growth and pathogenicity of Rhizopus, while hydroxypyridinone chelators have no effect Kidney Int, 45 (1994), pp. 667-671, 10.1038/ki.1994.89

[63]. B.J. Ferguson, T.G. Mitchell, R. Moon, E. M. Camporesi, J. Farmer Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis Rev Infect Dis, 10 (3) (1988 May-Jun), pp. 551-559, 10.1093/clinids/10.3.551 DOI: 10.1093/clinids/10.3.551