Management of mucormycosis

[1]Dr. Manshi Sagar , [2]Dr. Puja Bansal , [3]Dr. Deepak Bhargava

School Of Dental Sciences, Sharda University , Greater Noida, U.P, India (Review article)

Abstract: A zygomycete family opportunistic fungal infection called mucormycosis can result in a variety of illness.The majority of the time, the hosts have underlying problems that make them more susceptible to infection. Mortality increases noticeably, approaching 70–90% in cases of disseminated mucormycosis, depending on patient features (such as those of critically ill or immunocompromised individuals) and site of infection. In India, isolated renal mucormycosis has developed as a new clinical entity, and rhino-orbito-cerebral presentation accompanied with uncontrolled DM was the prevalent feature. Black fungus can enter a patient's body through sporangiospore ingestion, inhalation, or inoculation via wounds or trauma, inhalation of saturated oxygen, medical equipment, or an inadequate ventilation system.

Keywords: mucormycosis, zygomycete, fungal infection ,rhino-orbito- cerebral, epidemiology

Introduction

A zygomycete family opportunistic fungal infection called mucormycosis can result in a variety of illness. The majority of the time, the hosts have underlying problems that make them more susceptible to infection. Due to the fact that the causative fungus are common environmental organisms, immunocompetent people typically do not develop any symptoms.[1] It can affect immunocompetent hosts as well (such as trauma patients), despite the fact that it is typically classified as an opportunistic infection that preferentially affects people with diabetes mellitus (DM), neutropenia, malignancy, chronic renal failure, and acquired immunodeficiency syndrome. It also affects people who have had organ or hematopoietic stem cell transplants.[2][3]

Overall mucormycosis infection mortality is still high, ranging from 20 to 50%, despite rigorous surgical and polyene antifungal therapy. Mortality increases noticeably, approaching 70–90% in cases of disseminated mucormycosis, depending on patient features (such as those of critically ill or immunocompromised individuals) and site of infection. [4][5]

According to a recent projection for the years 2019-2020, mucormycosis prevalence ranged from 0.005 to 1.7 per million people worldwide, but in India, it is approximately 80 times higher (0.14 per 1000) than in wealthy nations [[6],[7], [8]]. To put it another way, India has the highest rate of mucormycosis in the entire world. Nevertheless, India was previously the world's diabetes capital and has the second-highest prevalence of diabetes mellitus (DM) in the world.[9]

Etiology

Mucor spp., Rhizopus spp., and Lichtheimia spp. (formerly Absidia and Mycocladus) spp. are the three most prevalent mucormycosis-causing organisms.[10] Uncontrolled diabetes mellitus, in particular ketoacidosis, steroid use, extreme ages, neutropenia, particularly with haematological malignancies, AIDS, renal failure, organ or stem cell transplantation, iron overload, skin trauma, broad-spectrum antibiotics, intravenous drug abuse, prophylactic voriconazole for aspergillosis, and malnutrition are risk factors.[11]

There are significant regional variations in the aetiology of mucormycosis. For instance, the most typical fungi found in mucormycosis patients in Europe were Rhizopus spp. (34%), Mucor spp. (19%), and Lichtheimia spp. (19%).[12] Apophysomyces elegans, A. variabilis, and Rhizopus homothallicus are emerging species in India, where Rhizopus species are the most frequent causes of the disease. Uncommon agents like Mucor irregularis and Thamnostylum lucknowense are also being documented.[13] [14] Mucormycosis is an infection caused by fungi belonging to the order Mucorales.[15] Due to lengthy hospital stays, a lack of medical personnel, and ensuing aseptic settings, the current COVID-19 pandemic scenario presents additional potential for disease entrance. In order to give oxygen to hypoxemic patients, mechanical ventilators have been identified as the most usual entrance point.[16]

Epidemiology

The majority of human infections are brought on by direct inoculation of organisms into damaged skin or mucosa or by inhalation of fungal sporangiospores that have been discharged into the air.[17] The Mucorales are widely distributed in nature, however it is unclear exactly what their ecology involves. They are thermotolerant and typically found in decomposing organic debris. There may be seasonal change in Mucorales infection.[18]

Between developed and developing nations, mucormycosis epidemiology appears to differ. The condition is still rare in wealthy nations and is now most common in people with diabetes mellitus, haematological malignancies (HMs), who are receiving chemotherapy, and people who have had allogeneic stem cell transplants.[19] The primary clinical manifestation of the disease in HM patients is pulmonary. [12, 20] In India, isolated renal mucormycosis has developed as a new clinical entity, and rhino-orbito-cerebral presentation accompanied with uncontrolled DM was the prevalent feature. The primary clinical manifestation of the disease in HM patients is pulmonary.[13] In a significant Mexican study that looked at 418 instances, diabetes was the underlying condition in 72% of patients and was linked to sinusitis. In the group of patients who had underlying malignancies, the pulmonary and sinus presentations were identical. [21]

Pathophysiology

Black fungus can enter a patient's body through sporangiospore ingestion, inhalation, or inoculation via wounds or trauma, inhalation of saturated oxygen, medical equipment, or an inadequate ventilation system.[22,23,24]An key part of Mucorales infection is played by phagocytes. Mononuclear or polymorphonuclear phagocytes can effectively combat the hyphae and spores of moulds that cause mucormycosis. Therefore, individuals with a very low phagocyte count or defective phagocytosis function are

more likely to contract black function infections.[25] Patients with severe neutropenia and those without phagocytic function are more likely to develop mucormycosis. However, it differs for AIDS patients.[26] .

Phagocytes are dysfunctional in the presence of hyperglycemia and low pH, which is seen in individuals with diabetic ketoacidosis (DKA), and they exhibit poor chemotaxis and defective intracellular death by both oxidative and nonoxidative processes.[27] Mucormycosis can absorb iron from the host for survival and reproduction as well as to carry out a variety of enzymatic functions. When using Rhizopus oryzae to test iron sequester activity, it was discovered that mucormycosis grows quickly in media containing iron but extremely poorly in serum devoid of iron.[28] Siderophores, which have a significant affinity and specificity to chelate iron molecules, are a low molecular weight molecule that are produced by bacteria or fungus. Fungi that have a significant affinity for iron and can separate it from ferritin and transferrin to use for life inside hosts create the siderophore deferoxamine.[29] Because of a unique mechanism used by mucormycosis to penetrate vascular endothelial cells, the infection spread from one area of the body to another. GRP78 receptors on cell surfaces became more active during glucose deprivation, acting as receptors for Mucorales in humans to kill endothelial cells.[30]

Clinical manifestation

Tissue necrosis caused by angioinvasion and subsequent thrombosis is the clinical hallmark of invasive mucormycosis. The infection usually progresses quickly and kills the patient unless the underlying risk factors (such as metabolic acidosis) are treated, antifungal medications are used aggressively, and surgical excision is performed. Invasive mucormycosis is divided into one of the six main clinical variants based on the anatomic site and clinical presentation: Rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and six unusual, rare types, including endocarditis, osteomyelitis, peritonitis, and renal infection[31,32,33]

Rodenet et al. evaluated 929 cases of mucormycosis and discovered that the most frequent sites of involvement were the sinuses (39%), lungs (24%), disseminated (23%) and skin and soft tissue infection (SSTI) (19%). In a different study, among 154 cancer patients, 92 (60%) had lung disease, and 6 (4%) had ROCM.[34]

Diagnosis

It is crucial to diagnose mucormycosis as soon as possible because doing so may improve the prognosis. Studies have revealed that it improves survival rates[35], and it may also lessen suffering, deformity, or the necessity for surgical resection. The best use of clinical microbiological technique, execution of molecular detection, expert assessment of cytological and histological data, utilisation of computed tomography (CT) in the early stages, and careful evaluation of clinical manifestations are all necessary for the diagnosis of mucormycosis.[36] Higher resolution computed tomography (CT) and magnetic resonance imaging can be very helpful for the diagnosis of pulmonary, rhino-orbital-cerebral, and disseminated mucormycosis.[37] . Eight patients with pulmonary mucormycosis had wedge-shaped consolidation or nodules on CT chest imaging, mostly in the posterior regions of the upper lobes of the lungs, but there were relatively few endobronchial lesions seen.[38] Histopathological evaluation and culture are reliable methods for determining whether someone has mucormycosis.[39,40] A black eschar or dead tissue may be visible on infected individuals with mucormycosis as a result of tissue infraction and blood vessel thrombosis.[41] Quantitative PCR in tissue or serum can be used to diagnose some species, such as Mucor, Rhizomucor, Rhizopus, and Lichtheimia, and it may be more effective than culture approach.[39,42-50]

Management of mucormycosis

The essential factor in controlling mucormycosis is early diagnosis. Early and prompt diagnosis is crucial for the efficacy of therapies, as is the elimination of risk factors for mucormycosis[51] Intravenous (IV) amphotericin B (lipid formulation) is the drug of choice for initial therapy.[52,53] . For individuals who have responded to amphotericin B, step-down therapy may involve the use of posaconazole or isavuconazole. For patients who don't respond to or are unable to tolerate amphotericin B, posaconazole or isavuconazole can also be used as salvage therapy; whether to use oral or IV posaconazole or isavuconazole for salvage therapy depends on the severity of the patient's illness, whether an initial course of amphotericin B could be given, and whether the patient has a healthy gastrointestinal (GI) tract.[56,57]

Surgery- A different approach of treating mucormycosis, particularly when soft tissue or the rhino-cerebral region is involved, is surgical debridement of the affected tissue.[54,55] As soon as a diagnosis of any type of mucormycosis is suspected, aggressive surgical debridement of the affected tissues should be taken into consideration. In anecdotal clinical assessments of rhinocerebral and pulmonary infection, surgical intervention with removal of necrotic tissue and debulking infection has been linked to better survival.[56,57] Debridement to remove all necrotic tissue in the case of a rhinocerebral infection can frequently be disfiguring and necessitate the removal of the orbit, palate, and nasal cartilage. But more recent research demonstrates that endoscopic debridement with minimal tissue removal is possible.[57]

Mucormycosis infection outcomes are improved by the early start of antifungal medication. This was demonstrated in a retrospective analysis of 70 patients with hematologic malignancies who also had mucormycosis, in which the mortality rate at 12 weeks following diagnosis increased by almost a factor of two due to delayed amphotericin B therapy (beginning treatment 6 days after diagnosis) (83 versus 49 percent).[58]

Amphotericin B lipid formulations are the major first-line treatment for mucormycosis (LFAB).[59,60] For infections of the central nervous system, the recommended dose of liposomal amphotericin B is 5 mg/kg/day, and it can go as high as 10 mg/kg/day. Patients in the French Mycosis Study Group's AmbiZygo study received 10 mg/kg/day of liposomal amphotericin B for the first month of treatment, along with surgery as needed. Between weeks 4 and 12, the overall response rate increased from 36% to 45%. 40% of patients had renal function impairment, which was evident by the serum creatinine level doubling (although 63% saw a brief increase).[61] Antifungal agent dosage recommendations continue to be a contentious topic. For triazoles like posaconazole and isavuconazole, this is valid. The ESCMID/ECMM guidelines suggest posaconazole be used as first-line treatment (moderate recommendation) at a dose of 200 mg of the oral suspension every six hours, in contrast to ECIL-6's advice that it be used as salvage

or maintenance therapy. Posaconazole's introduction in intravenous and tablet form has boosted the drug's bioavailability and exposure to more people.[62]

A recently formed triazole called isavuconazole has a broad spectrum of antifungal action, including Mucorales.[63] Isavuconazole 200 mg once daily (qd) (after six doses of 200 mg q8h) was given to 21 patients with mucormycosis as the primary treatment in a multicenter, open-label trial (VITAL trial). These patients were matched with contemporaneous controls from a registry of rare fungal diseases who had received conventional or lipid amphotericin B at a median dose of 70 or 325 250 mg qd, respectively,[64] Isavuconazole was therefore considered to be a substitute to amphotericin B as the first-line treatment for mucormycosis because the results in the two groups were comparable. Despite the positive findings, the study's limitations—namely, its small size and the matching of external controls—should be taken into consideration.[65]

The use of hyperbaric oxygen in an effort to create a more oxygen-enriched cell environment and the injection of cytokines concurrently with the antifungal medication are two other adjuvant therapies. Granulocyte-macrophage colony-stimulating factor and/or interferon-γ may boost the immune response against specific Mucorales, which may help treat the infection, according to in vitro and some preclinical findings.[66,67] however, these therapies should be utilized cautiously because there are no clinical studies on their use.

Iron chelators are an additional therapy option for mucormycosis. Deferasirox, an iron chelating drug, was discovered to boost survival rates in mice with mucormycosis and diabetic ketoacidosis in a murine model.[68] Deferasirox along with LFAB is also effective in rhinoorbital cerebral mucormycosis patients.[69]

REFERENCES

1. Binder U,Maurer E,Lass-Flörl C, Mucormycosis--from the pathogens to the disease. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2014
2. S. R. Sridhara, G. Paragache, N. K. Panda, and A. Chakrabarti, "Mucormycosis in immunocompetent individuals: an increasing trend," Journal of Otolaryngology, vol. 34, no. 6, pp. 402–406, 2005.
3. Mallis, S. N. Mastronikolis, S. S. Naxakis, and A. T. Papadas, "Rhinocerebral mucormycosis: an update," European Review for Medical and Pharmacological Sciences, vol. 14, no. 11, pp. 987–992, 2010.
4. M. D. Zilberberg, A. F. Shorr, H. Huang, and et al, "Hospital days, hospitalization costs, and inpatient mortality among patients with mucormycosis: a retrospective analysis of US hospital discharge data," BMC Infectious Diseases, vol. 14, article 310, 2014.
5. M. M. Roden, T. E. Zaoutis, W. L. Buchanan et al., "Epidemiology and outcome of zygomycosis: a review of 929 reported cases," Clinical Infectious Diseases, vol. 41, no. 5, pp. 634–653, 2005.
6. Skiada, I. Pavleas, M. Drogari-ApiranthitouEpidemiology and diagnosis of mucormycosis:
7. J. Chander, M. Kaur, N. Singla, et al.
8. Mucormycosis: battle with the deadly enemy over a five-year period in India
9. H. Prakash, A. Chakrabarti Global epidemiology of mucormycosis
10. J Fungi, 5 (2019), p. 26
11. International Diabetes FederationIdf diabetes atlas
12. Petrikkos G, Skiada A, Lortholary O et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012; 54: S23–S34.
13. Rammaert B, Lanternier F, Poirée S, Kania R, Lortholary O. Diabetes and mucormycosis: a complex interplay. Diabetes & metabolism, 2012; 38(3): 193-204
14. Skiada A, Pagano L, Groll A et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin Microbiol Infect. 2011; 17: 1859–1867.
15. Chakrabarti A, Singh R. Mucormycosis in India: unique features. Mycoses. 2014; 57: 85–90.
16. Chander J, Stchigel AM, Alastruey-Izquierdo A et al. Fungal necrotizing fasciitis, an emerging infectious disease caused by Apophysomyces (Mucorales). Rev Iberoam Micol. 2015; 32: 93–98.
17. Hibbett DS, Binder M, Bischoff JF, et al. A higher-level phylogenetic classification of the Fungi. Mycol Res. 2007;111:509–47.
18. Dallalzadeh LO, Ozzello DJ, Liu CY, Kikkawa DO, Korn BS. Secondary infection with rhino-orbital cerebral mucormycosis associated with COVID-19. Orbit. 2021;2021:1-4.
19. Ibrahim A, Edwards JEJr, Filler SG. , Mucormycosis, 2004PhiladelphiaHarcourt Brace
20. Talmi YP, Goldschmeid-Reouven A, Bakon M, et al. Rhino-orbital and rhino-orbitocerebral mucormycosis, Otolaryngol Head Neck Surg, 2002, vol. 127 (pg. 22-31
21. Spellberg B, Edwards JJr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management, Clin Microbiol Rev, 2005, vol. 18 (pg. 556-69
22. Klimko N, Khostelidi S, Volkova A et al. Mucormycosis in haematological patients: case report and results of prospective study in Saint Petersburg, Russia. Mycoses. 2014; 57: 91–96.
23. Corzo-Leon DE, Chora-Hernandez LD, Rodriguez-Zulueta P, Walsh TJ. Diabetes mellitus as the major risk factor for mucormycosis in Mexico: epidemiology, diagnosis, and outcomes of reported cases. Med Mycol. 2017; doi:
24. Lelievre L, Garcia-Hermoso D, Abdoul H, Hivelin M, Chouaki T, Toubas D, et al. Posttraumatic mucormycosis: A nationwide study in France and review of the literature. Med (United States) [Internet]. 2014 Nov 1 [cited 2021 May 30];93(24):395–404. Available from: /pmc/articles/PMC4602436/

25. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect 26 Dis. 2012;54(SUPPL. 1):23–34
26. Sipsas N V., Kontoyiannis DP. Occupation, lifestyle, diet, and invasive fungal infections [Internet]. Vol. 36, Infection. Infection; 2008 [cited 2021 May 30]. p. 515–25. Available from: https://pubmed.ncbi.nlm.nih.gov/18998051/
27. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J Clin Invest [Internet]. 1984 [cited 2021 May 30];74(1):150–60. Available from: /pmc/articles/PMC425195/?report=abstract
28. 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
29. Chinn RY, Diamond RD. Generation of chemotactic factors by Rhizopus oryzae in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis.
30. Ibrahim AS, Spellberg B, Edwards J. Iron acquisition: A novel perspective on mucormycosis pathogenesis and treatment [Internet]. Vol. 21, Current Opinion in Infectious Diseases. NIH Public Access; 2008 [cited 2021 May 30]. p. 620–5. Available from: /pmc/articles/PMC2773686/
31. De Locht M, Boelaert JR, Schneider YJ. Iron uptake from ferrioxamine and from ferrirhizoferrin by germinating spores of rhizopus microsporus. Biochem Pharmacol [Internet]. 1994 May 18 [cited 2021 May 30];47(10):1843–50. Available from: https://pubmed.ncbi.nlm.nih.gov/8204101/
32. Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest [Internet]. 2010 Jun 1 [cited 2021 May 30];120(6):1914– Alom et al
A. Goodman NL, Rinaldi MG. Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadoomy HJ. Agents of mucormycosis, Manual of clinical microbiology, 19915th edWashington, DCASM Press(pg. 674-92)
33. Lopes JO, Pereira DV, Streher LA, Fenalte AA, Alves SH, Benevenga JP. Cutaneous mucormycosis caused by Absidia corymbifera in a leukemic patient, Mycopathologia, 1995, vol. 130 (pg. 89-92)
A. Stas KJF, Louwagie GLH, Van Damme BJC, Coosemans W, Waer M, Vanrenterghem YFC. Isolated mucormycosis in a bought living unrelated kidney transplant, Transplant Int, 1996, vol. 9 (pg. 600-2
34. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases [Internet]. Vol. 41, Clinical Infectious Diseases. Oxford Academic; 2005 [cited 2021 May 30]. p. 634–53. Available from: https://academic.oup.com/cid/article/41/5/634/327691
35. Chamilos, G.; Lewis, R.E.; Kontoyiannis, D.P. Delaying Amphotericin B–Based Frontline Therapy Significantly Increases Mortality among Patients with Hematologic Malignancy Who Have Zygomycosis. Clin. Infect. Dis. 2008, 47, 503–509. [Google Scholar] [CrossRef]
36. Walsh, T.J.; Gamaletsou, M.N.; McGinnis, M.R.; Hayden, R.T.; Kontoyiannis, D.P. Early Clinical and Laboratory Diagnosis of Invasive Pulmonary, Extrapulmonary, and Disseminated Mucormycosis (Zygomycosis). Clin. Infect. Dis. 2012, 54, S55–S60. [Google Scholar] [CrossRef] [PubMed]
37. Severo CB, Guazzelli LS, Severo LC. Chapter 7 - zygomycosis. J Bras Pneumol [Internet]. 2010 [cited 2021 May 30];36(1):134–41. Available from: https://pubmed.ncbi.nlm.nih.gov/20209316/
38. Jamadar DA, Kazerooni EA, Daly BD, White CS, Gross BH. Pulmonary zygomycosis: Ct appearance. J Comput Assist Tomogr [Internet]. 1995 [cited 2021 May 30];19(5):733–8. Available from: https://pubmed.ncbi.nlm.nih.gov/7560318
39. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis [Internet]. 2012 Feb 1 [cited 2021 May 30];54(SUPPL. 1). Available from: https://pubmed.ncbi.nlm.nih.gov/22247446/
40. Hamilos G, Samonis G, Kontoyiannis DP. Pulmonary mucormycosis. Semin Respir Crit Care Med [Internet]. 2011 [cited 2021 May 30];32(6):693–702. Available from: https://pubmed.ncbi.nlm.nih.gov/22167397/
41. Venkatesh D, Dandagi S, Chandrappa P, Hema KN. Mucormycosis in Review on mucormycosis 30 immunocompetent patient resulting in extensive maxillary sequestration. J Oral Maxillofac Pathol [Internet]. 2018 Jan 1 [cited 2021 May 30];22(4):S112–6. Available from: /pmc/articles/PMC5824503
42. Lackner M, Caramalho R, Lass-Flörl C. Laboratory diagnosis of mucormycosis: Current status and future perspectives [Internet]. Vol. 9, Future Microbiology. Future Medicine Ltd.; 2014 [cited 2021 May 30]. p. 683–95. Available from: https://pubmed.ncbi.nlm.nih.gov/24957094/
43. Rickerts V, Mousset S, Lambrecht E, Tintelnot K, Schwerdtleger R, Presterl E, et al. Comparison of histopathological analysis, culture, and polymerase chain reaction assays to detect invasive mold infections from biopsy specimens. Clin Infect Dis [Internet]. 2007 Apr 15 [cited 2021 May 30];44(8):1078–83. Available from: https://pubmed.ncbi.nlm.nih.gov/17366453/
44. Bialek R, Konrad F, Kern J, Aepinus C, Cecenas L, Gonzalez GM, et al. PCR based identification and discrimination of agents of mucormycosis and aspergillosis in paraffin wax embedded tissue. J Clin Pathol [Internet]. 2005 Nov [cited 2021 May 30];58(11):1180–4. Available from: https://pubmed.ncbi.nlm.nih.gov/16254108/
45. Gholinejad-Ghadi N, Shokohi T, Seifi Z, Aghili SR, Roilides E, Nikkhah M, et al. Identification of Mucorales in patients with proven invasive mucormycosis by polymerase chain reaction in tissue samples. Mycoses [Internet]. 2018 Dec 1 [cited 2021 May 30];61(12):909–15. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/myc.12837
46. Salehi E, Hedayati MT, Zoll J, Rafati H, Ghasemi M, Doroudinia A, et al. Alom et al. 31 Discrimination of aspergillosis, mucormycosis, fusariosis, and scedosporiosis in formalin-fixed paraffin-embedded tissue specimens by use of multiple real-time quantitative PCR assays. J Clin Microbiol [Internet]. 2016 Nov 1 [cited 2021 May 30];54(11):2798–803. Available from: https://pubmed.ncbi.nlm.nih.gov/27605714/

47. Shigemura T, Nishina S, Nakazawa H, Matsuda K, Yaguchi T, Nakazawa Y. Early detection of Rhizopus DNA in the serum of a patient with rhinoorbital-cerebral mucormycosis following allogeneic hematopoietic stem cell transplantation [Internet]. Vol. 103, International Journal of Hematology. Springer Tokyo; 2016 [cited 2021 May 30]. p. 354–5. Available from: https://link.springer.com/article/10.1007/s12185-016-1938-x
48. . Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis [Internet]. Vol. 56, Medical Mycology. Oxford University Press; 2018 [cited 2021 May 30]. p. S93–101. Available from: /pmc/articles/PMC6251532/
49. Hammond SP, Bialek R, Milner DA, Petschnigg EM, Baden LR, Marty FM. Molecular methods to improve diagnosis and identification of mucormycosis. J Clin Microbiol [Internet]. 2011 Jun [cited 2021 May 30];49(6):2151–3. Available from: https://pubmed.ncbi.nlm.nih.gov/21508149/
50. Millon L, Herbrecht R, Grenouillet F, Morio F, Alanio A, Letscher-Bru V, 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 [Internet]. 2016 Sep 1 [cited 2021 May 30];22(9):810.e1-810.e8. Available from: https://pubmed.ncbi.nlm.nih.gov/26706615/
51. Riley TT, Muzny CA, Swiatlo E, Legendre DP. Breaking the Mold. Ann Pharmacother [Internet]. 2016 Sep 19;50(9):747–57. Available from: http://journals.sagepub.com/doi/10.1177/1060028016655425
52. McCarthy M, Rosengart A, Schuetz AN, et al. Mold infections of the central nervous system. N Engl J Med 2014; 371:150.
53. Cornely OA, Alastruey-Izquierdo A, Arenz D, 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 2019; 19:
54. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect [Internet]. 2014 [cited 2021 May 30];20(S3):5–26. Available from: https://pubmed.ncbi.nlm.nih.gov/24479848/
55. Giudice G, Cutrignelli D, Sportelli P, Limongelli L, Tempesta A, Gioia G, et al. Rhinocerebral Mucormycosis with Orosinusal Involvement: Diagnostic and Surgical Treatment Guidelines. Endocrine, Metab Immune Disord Targets [Internet]. 2017 Feb 22 [cited 2021 May 30];16(4):264–9. Available from: https://pubmed.ncbi.nlm.nih.gov/28017141/
56. Sun HY, Aguado JM, Bonatti H, et al. Pulmonary zygomycosis in solid organ transplant recipients in the current era. Am J Transplant 2009; 9:2166.
57. Sun HY, Forrest G, Gupta KL, et al. Rhino-orbital-cerebral zygomycosis in solid organ transplant recipients. Transplantation 2010; 90:85.
58. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis 2008; 47:503.
59. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect [Internet]. 2014 [cited 2021 May 30];20(S3):5–26. Available from: https://pubmed.ncbi.nlm.nih.gov/24479848
60. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis [Internet]. Vol. 56, Medical Mycology. Oxford University Press; 2018 [cited 2021 May 30]. p. S93–101. Available from: /pmc/articles/PMC6251532/
61. 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: 3116–3123
62. Wiederhold NP. Pharmacokinetics and safety of posaconazole delayed-release tablets for invasive fungal infections. Clin Pharmacol. 2016; 8: 1–8.
63. Rybak JM, Marx KR, Nishimoto AT, Rogers PD. Isavuconazole: pharmacology, pharmacodynamics, and current clinical experience with a new triazole antifungal agent. Pharmacother. 2015; 35: 1037–1051.
64. Marty FM, Ostrosky-Zeichner L, Cornely OA et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016; 16: 828–837
65. Roilides E, Antachopoulos C. Isavuconazole: an azole active against mucormycosis. Lancet Infect Dis. 2016; 16: 761–762
66. Gil-Lamaignere C, Simitsopoulou M, Roilides E et al. Interferon- gamma and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important zygomycetes. J Infect Dis. 2005;191: 1180–1187.
67. Roilides E, Antachopoulos C, Simitsopoulou M. Pathogenesis and host defence against Mucorales: the role of cytokines and interaction with antifungal drugs. Mycoses. 2014; 57: 40–47.
68. Ibrahim AS, Gebremariam T, Lin L, Luo G, Husseiny MI, Skory CD, et al. The high affinity iron permease is a key virulence factor required for Rhizopus oryzae pathogenesis. Mol Microbiol [Internet]. 2010 [cited 2021 May 30];77(3):587–604. Available from: https://pubmed.ncbi.nlm.nih.gov/20545847/
69. Reed C, Ibrahim A, Edwards JE, Walot I, Spellberg B. Deferasirox, an ironchelating agent, as salvage therapy for rhinocerebral mucormycosis [2] [Internet]. Vol. 50, Antimicrobial Agents and Chemotherapy. Antimicrob Agents Chemother; 2006 [cited 2021 May 30]. p. 3968–9. Available from: https://pubmed.ncbi.nlm.nih.gov/17000743/