Review Article

Mucormycosis: Issues, Pathophysiology, Diagnosis and Treatment

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ABSTRACT

Mucormycosis (Black fungus) is an infection caused by opportunistic fungi of order Mucorales affecting the immune-compromised individuals. Cases of Aspergillus and Candida (White fungus) were also reported. The cases of fungal co-infection in COVID-19 patients are increasing globally affecting mainly diabetic patients and individuals that have undergone corticosteroid therapy. Iron metabolism and hypoxia plays an important role in pathophysiology of this disease. Mucormycosis causes thrombosis of blood vessels hindering the blood circulation causing black discoloration of affected site. Histopathological examination of specimen is the most effective way of its diagnosis. Surgical removal of affected site is the best treatment practice in rhino-orbital and cutaneous cases whereas lipid formulation of Amphotericin B is effective in other forms of fungal infection.

Keywords: Mucormycosis; Immuno-compromised; Rhino-orbital; Amphotericin B

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INTRODUCTION

COVID-19 is a viral disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 belonging to coronaviridae family. Airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, type II pneumocytes and macrophages are the primary target sites of SARS-CoV-2 virus.[1] High glucose level in diabetic patients, ketoacidosis, and low oxygen environment inside host body provides favorable condition for the virus to replicate in COVID-19 infected patient using host metabolism.

Phycomycosis or zygomycosis was first described in 1885 by Paltauf and was later coined by Baker, an American pathologist, in 1957 as Mucormycosis.[2] Mucormycosis is a rare type of life threatening invasive fungal infection in immune-compromised hosts caused by species of order Mucorales, phylum Zygomycota and subphylum Mucoromycotina and are generally found in soil containing decaying organic matter, such as leaves compost piles or rotten wood.[3] *Rhizopus oryzae* is responsible for almost 70% of all cases of mucormycosis.[4]

Table 1: Etiological agents responsible for mucormycosis[5]

Family	Genus	Species

Mucoraceae	*Absidia* *Apophysomyces* *Mucor* *Rhizopus*	*A corymbifera* *A elegans* *M circinelloides* *M hiemalis* *M racemosus* *M ramosossomus* *M rouxianus* *R pusillus* *R arrhizus (oryzae)*(most common) *R azygosporus*
Cunninghamellaceae	*Cunninghamella*	*C. bertholletiae*
Mortierellaceae	*Mortierella*	
Saksenaceae	*Saksenaea*	*S. vasiformis*
Syncephalastraceae	*Syncephalastrum*	*S. racemosum*
Thamnidaceae	*Cokeromyces*	*C. recurvatu*

Aspegillus and *Candida* species causes infection known as **"White fungus"**. ***Aspergillus fumigatus*** is the most notorious fungus endemic in Southeast Asia causing systemic infections and COVID-19 associated pulmonary aspergillosis patients particularly in immuno-compromised individuals such as HIV-positive patients or patients with impaired cell-mediated immunity.[6] Cases of white fungus is rarer than black fungus but possess higher mortality rate. Candida species (***C albicans***: **most common)** is a harmless commensal present as normal flora on skin and inside the body like mouth, throat, vagina gut etc. It remains harmless until any breaches are found in skin or internal organs or any natural defense mechanism in that site of infection.

Table 2: Classification of Aspergillus[7] and Candida[8]

Classification	**Aspergillus**	**Candida**
Kingdom	Fungi	Fungi
Phylum	*Ascomycota*	*Ascomycota*
Class	*Eurotiomycetes*	*Saccharomycetes*
Order	*Eurotiales*	*Saccharamycetales*
Family	*Trichocomaceae*	*Debaryomycetaceae*
Genus	*Aspergillus*	*Candida*
Species	*Aspergillus fumigatus*	*Candida albicans*

Overall Epidemiology of Mucormycosis and other fungal co-infection

Mucorales are ubiquitous in nature, so is the cases of mucormycosis. Globally, the incidence rate of mucormycosis fluctuates from 0.005 to 1.7 per million population[9] whereas, in Indian population its prevalence is 0.14 per 1000 i.e., about 80 times higher than developed countries.[10] According to the estimate of Leading International Fungal Education (LIFE), the annual prevalence of mucormycosis might be around 10,000 cases in the world excluding India and reaches 910,000 cases globally including the cases in India.[11] The cases of mucormycosis is waxing rapidly globally but the growth rate is higher in Asian countries like India and China. However, W. Jeong *et al.*, revealed that the prevalence of disease to be 34% in Europe, followed by Asia (31%) and North or South America (28%), Africa (3%), Australia and New Zealand (3%) based on a recent review of 851 cases over the period January 2000 through January 2017.[12] The most common risk factor associated with the disease was found to be Diabetes Mellitus in Asian continent and hematological malignancies and transplantation European countries and US.[13,14] The cases of nosocomial mucormycosis are also increasingly being reported after the use of contaminated wooden tongue depressors, umbilical catheter, bandages etc.[15]

Chen et al. performed fungal culture on all 99 COVID-19 patients and discovered five cases of fungal infection out of which *Aspergillus flavus*, *Candida glabrata* and *C. albicans* causes one, one and three cases respectively.[16] Five cases of COVID-19 associated

invasive pulmonary aspergillosis (IPA) was found among 19 consecutive critically ill patients with moderate to severe ARDS in study performed by Germans.[17] Among 31 ICU patients 5 out of 6 presumed IPA patients were found to have fungal infection associated with *A. fumigatus* in Netherlands.[18]

Pathophysiology

This disease is not contagious and no cases of transmission through contact between humans or animals have been reported yet. However, the fungal spores i.e., sporangiospores plays pivotal role in its occurrence.[19] Lower respiratory infection by SARS-CoV-2 causes diffuse alveolar damage with severe inflammatory exudation and patients always have immunosuppression with a decrease in CD4 + T and CD8 + T cells.[20] So corticosteroids like Methylprednisolone and Dexamethasone were used to ameliorate inflammation mediated lung injury and reduce chances of respiratory failure in COVID-19 patients.[21] Major risk factors that possess higher susceptibility to fungal co-infection includes use of corticosteroids as immunosuppressant during organ transplantation, uncontrolled diabetes (diabetic ketoacidosis) and other forms of metabolic acidosis, cancer, neutropenia, trauma, etc.[22] The mortality rate of mucormycosis varies between 40-80% based on the underlying condition and site of infection.[23] Suspected fungal infection requires immediate medical attention as it may affect the entire body through hematogenous route and leads to progressive and destructive nature of infection.

After the entry of spores through cutaneous route or entry into the lungs after angio-invasion, the spores must pass through the mononuclear and poly-nuclear phagocytes and are terminated by the oxidative factors and defensins manufactured by the host cell in immune-competent organisms. The angio-invasion results in thrombosis inside blood vessel and subsequent tissue necrosis. But in case of immune-compromised organism, the movement of factors produced as defense against fungal infection is impeded.[24]

1. Diabetes

Mucorales possess a virulence factor that possess ability to acquire iron from the host as it is an essential element for cell growth and development.[25] An iron is bound to host carrier proteins i.e., transferrin, ferritin, and lactoferrin and avoids the availability of free iron in the circulation which possess toxic effect.[26] The strategy of iron sequestration is a major host defense mechanism against microbes and against Mucorales in particular. In patients with Diabetic ketoacidosis, the level of free iron in their serum is elevated and possess higher susceptibility to mucormycosis.[27] Use of deferoxamine in patients also increases the incidence of mucormycosis because this chelant is used as a siderophore by Mucorales to obtain more iron.[28] This theory has been proved and well-known that administering iron or deferoxamine to animals infected with Mucorales reduces their survival.[29]

2. Starvation

A study revealed that *Mucorales* adhere to the extracellular matrix laminin and type IV collagen ultimately leading to angio-invasion. Glucose-regulated protein (GRP78) was found to act as a receptor that mediates penetration through and damage of endothelial cells by Mucorales which was later identified to be induced by glucose starvation. **Research performed on a mouse model explained that the enhanced expression of GRP78 leads to increased endocytosis of fungal species by human endothelial cells and their damage.**[30] So, starvation also acts as a predisposing factor leading to mucormycosis.

3. Organ transplantation

Mucormycosis constitutes a small proportion of invasive fungal infections in solid organ transplant (SOT) recipients and the estimated incidence ranges from 0.4% to 16.0% depending on the type of organ transplanted:[31]

- 0.2%– 1.2% in renal transplant recipients
- 0%–1.6% in liver transplant recipients
- 0%–0.6% in heart transplant recipients
- 0%–1.5% in lung transplant recipients

All recipients underwent chronic immunosuppression with high doses of systemic corticosteroids. Dissemination of infection was found to occur in cases where the transplanted organ was rejected by the host immune system.[32]

So, understanding of mechanism by which the fungus disseminates and damages the structures on its route is imperative to develop approaches to treat and prevent fungal infections.

Forms of fungal infection and symptoms

Fungal infections are of multiple types based on its route of exposure and signs of fungal infection also depends

on the type of fungal infection and parts of the organ associated with it.

- **Pulmonary or sinus form**: This form mainly affects the lungs, sinuses, eyes, and face as exposure occurs by inhaling fungal spores or sporangiospores from the environment.[33] In rare cases, the infection can spread to the central nervous system. Fever, headache, and sinus pain are the major symptoms of sinus form along with coughing in case of Lung infections.[34]
- **Cutaneous form**: It is the most common form of fungal infection in case of immuno-competent organisms and the fungus can enter the skin through the various forms of trauma on the skin like cuts, scrapes, puncture wounds, or other forms.[35] In case of cutaneous form of infection, the tissue undergoes necrosis leading to the black discoloration of affected tissue i.e., "Black fungus". Fever, and tenderness, pain, heat, excessive redness, or swelling around a wound are the other symptoms associated with cutaneous form of infection.[36]

The above-mentioned forms are most seen in COVID-19 patients. Some rarely seen cases are:

- **Gastrointestinal form**: It is the type of infection generally affecting neonates and can show symptoms like other gastro-intestinal diseases and possess higher mortality rate.[37]
- **Nervous form**: This is the progressive form of rhino-orbital mucormycosis whereas some cases associated with intravenous drug addicts are also encountered. Meningitis was found to the non-specific sign associated with it.[38]

Table 3: Various forms of fungal infection with their underlying factors

S.N.	Forms of fungal infection	Predisposing factors	References
1	Pulmonary	Neutropenia, corticosteroid therapy	39
2	Cutaneous	Trauma, diabetes	40
3	Gastrointestinal	Malnutrition	41
4	Rhino-cerebral (most common)	Diabetes, ketoacidosis	4
5	Disseminated disease	Deferoxamine, neutropenia, corticosteroids	42

Other symptoms associated with fungal infection:

- Sinusitis – nasal blockade or congestion, blackish or bloody nasal discharge
- Toothache, loosening of teeth, jaw involvement.
- Blurred vision
- Chest pain
- Hemoptysis, worsening of respiratory symptoms.

Diagnosis of fungal infection

Rhino-orbital and mucocutaneous mucormycosis is relatively easy to diagnose than the condition when deeper tissues are invaded like in case of pulmonary mucormycosis.[43] Aggressive processing of the specimen before plating, especially when the samples are biopsy specimens, leads to reduced sensitivity of tests.[44]

- **Fungal culture**

Microbiology of Mucorales

- Mucorales grow rapidly forming 'cotton candy-like' mycelium on both non-selective and selective media to cover the entire plate in only a few days.
- Hyaline appearance, vigorous growth, light coloration on the reverse side of the plate (tan to yellow for most species) and variable degrees of coloration on the sporulating surface of the colonies (from pure white to tan, brown, grey, or even black) are the major macroscopic features of Mucorales.

Despite the use of this technique, many false negative results have been reported compared to histopathological examination.

- **Histopathology**
- **Suspected:** Based on results of direct microscopy of clinical specimens, preferably stained with fluorescent brighteners.
- **Confirmation**: Non-pigmented hyphae showing tissue invasion must be present in tissue sections-stained with Haematoxylin-Eosin (HE), or Periodic Acid Schiff stain (PAS)

The main diagnostic approach for confirmation of mucormycosis involves the detection of the invasion of

vessels by wide and non-septate hyphae branched at right angles during histologic examination.[45]

Note: Similarly other major fungal infections associated with COVID-19 patients must be determined and the Ascomycetes group of fungi causing "White fungus" typically appears as:

- The diagnostic feature of Candida albicans is the formation of germ tubes along with creamy-grey colonies filamenting along their outer border.[46]
- Apergillus species shows slender septate hyphae that exhibit angular dichotomous branching[47]

Results obtained from culture of clinical samples and various clinical data must be studied to reach final decision.[48]

- **Radiographic examination**

The efficacy of radiographic diagnosis depends on the presence of imaging techniques, tools, and trained personnel as the diagnosis by imaging is difficult to perform. Simple radiology and CT-scans usually show invasion of the sinuses, displacement of the orbit and invasion of the surrounding bone structures in cases of rhino-orbital lesions. Similarly, magnetic resonance imaging is the technique of choice when intra-cranial structures are affected.[5]

Treatment

Various treatment approaches are considered during treatment based on the condition of patient and nature of infection.

➢ **Surgical**

Rapid and complete surgery proves to be better than partial resection of necrotic tissue in cutaneous and rhino-orbital form of mucormycosis. It is impossible to operate in pulmonary and disseminated cases of mucormycosis.[49] Irrigation of surgical site with Amphotericin-B has also been done to mitigate the vaso-occlusive nature of infection which might impede the flow of antibiotics to the site of infection.[50]

➢ **Anti-fungal therapy**

- **Polyenes**:

Amphotericin B deoxycholate (AMP) remains the only licensed antifungal agent for mucormycosis whereas the lipid formulations of amphotericin B are also considered a safe and efficient alternative. Starting doses recommended for the lipid formulation of amphotericin are 5-7.5 mg/kg/day and higher dosages up to 10 mg/kg/day for cases with CNS involvement.[51] Liposomal amphotericin B has lower toxicity and better tolerated than any other formulations.[52]

- **Azoles:**

Table 4: Different anti-fungal drugs of azoles group

S.N.	Name	Efficacy	References
1	Itraconazole	Possess in-vitro activity against Mucorales but evidence of failure has also been reported.	[53]
2	Voriconazole	Not active in-vitro against Mucorales	[54]
3	Posaconazole and Ravuconazole	Possess higher efficacy than itraconazole but less effective than Amphotericin B deoxycholate	[55]

➢ **Iron chelation therapy**

Iron chelators other than Deferoxamine, like Deferasirox and deferiprone have been proved to be effective agents against mucormycosis in animal models and deferasirox has also been used successfully as salvage therapy in a case of rhinocerebral mucormycosis.[56]

➢ **Others**

Granulocyte stimulating factor and hyperbaric oxygen were also found to be used as a supportive treatment against mucormycosis along with mainline drugs.[57]

Note: Amphotericin B is well known kidney toxicity, so BGS005 is being used against the fungus as a safe alternative in India.[58]

Table 5: Antifungal therapy used to treat fungal infection in COVID-19 patients.

Country	Age	Sex	Fungal species	Comorbidity	Treatment	Outcome	References
India	52yr	M	Rhizopus arrhizus	Type-2 Diabetes mellitus	Liposomal Amp B	Follow-up	[59]
India	33yr	F	Rhizopus arrhizus	Asthma Hypertension	Liposomal Amp B	Dead	[60]
India	68yr	F	Rhizopus arrhizus	Type-2 Diabetes mellitus	Liposomal Amp B	Dead	[61]
Pakistan	81yr	M	Aspergillus flavus	Diabetes mellitus	Amphotericin B	Dead	[62]
Pakistan	85yr	F	Aspergillus niger	Diabetes mellitus, Hypertension	Voriconazole	Dead	[62]
Pakistan	46yr	M	Aspergillus niger	Diabetes mellitus	No antifungal	Discharged	[62]

Conclusion

Fungal infection in immune-compromised patients is a life-threatening condition producing thrombosis inside blood vessel leading to necrotized black discoloration of infected site mainly affecting sinuses, lungs, skin, gut and various other parts of the body. New diagnostic tools must be discovered to detect the fungus and treat the patient in time. In recent scenario, co-infection with fungus in COVID-19 patients had led to the deaths of multiple individuals. So, effective study must be done to tackle with this disease in coming days.

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REFERENCES

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273. [Google scholar]

2. Baker RD. Mucormycosis Mucormycosis Intestinal mucormycosis presents as hemorrhagic Organism .— Rhizopus ,. Published online 2015:1954-1957. DOI: 10.1001/jama.1957.02970450007003 [PubMed]

3. Estados Unidos. Center for Diseases Control and Prevention (CDC). Mucormycosis : The Basics. Published online 2011:2011. [Full text]

4. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clinical Infectious Diseases*. 2005;41(5):634-653.[Google Scholar]

5. Bouza E, Muñoz P, Guinea J. Mucormycosis: An emerging disease? *Clinical Microbiology and Infection*. 2006;12(SUPPL. 7):7-23. doi:10.1111/j.1469-0691.2006.01604.x [Google Scholar]

6. Kwon-Chung KJ, Sugui JA. Aspergillus fumigatus—what makes the species a ubiquitous human fungal pathogen? *PLoS Pathog*. 2013;9(12):e1003743. [PubMed]

7. Tsang CC, Tang JYM, Lau SKP, Woo PCY. Taxonomy and evolution of Aspergillus, Penicillium and Talaromyces in the omics era – Past, present and future. *Comput Struct Biotechnol J*. 2018;16:197-210. doi: 10.1016/j.csbj.2018.05.003 [Google Scholar]

8. McGinnis MR, Ajello L, Beneke ES, et al. Taxonomic and nomenclatural evaluation of the genera Candida and Torulopsis. *J Clin Microbiol*. 1984;20(4):813-814. doi:10.1128/jcm.20.4.813-814.1984 [Google Scholar]

9. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. *Journal of Fungi*. 2019;5(1):26. [PMC]

10. Chander J, Kaur M, Singla N, et al. Mucormycosis: battle with the deadly enemy over a five-year period in India. *Journal of Fungi*. 2018;4(2):46. [Google Scholar]

11. Chakrabarti A, Dhaliwal M. Epidemiology of mucormycosis in India. *Curr Fungal Infect Rep*. 2013;7(4):287-292.[Google Scholar]

12. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clinical Microbiology and Infection*. 2019;25(1):26-34. [Google Scholar]

13. Chakrabarti A, Das A, Sharma A, et al. Ten years' experience in zygomycosis at a tertiary care centre in India. *Journal of Infection*. 2001;42(4):261-266. [Google Scholar]

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. *Clinical Microbiology and Infection*. 2011;17(12):1859-1867. [Google Scholar]

15. Holzel H, Macqueen S, MacDonald A, et al. Rhizopus microsporus in wooden tongue depressors: a major threat or minor inconvenience? *Journal of Hospital Infection*. 1998;38(2):113-118. [Google Scholar]

16. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The lancet*. 2020;395(10223):507-513. [Full Text]

17. Koehler P, Cornely OA, Böttiger BW, et al. COVID-19 associated pulmonary aspergillosis. *Mycoses*. 2020;63(6):528-534. [PubMed]

18. van Arkel ALE, Rijpstra TA, Belderbos HNA, Van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19–associated pulmonary aspergillosis. *Am J Respir Crit Care Med*. 2020;202(1):132-135. [PubMed]

19. Kwon-Chung KJ, Bennett JE. Medical mycology. *Rev Inst Med Trop Sao Paulo*. 1992;34(6):504. [Google Scholar]

20. Yang W, Cao Q, Qin LE, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *Journal of Infection*. 2020;80(4):388-393. [Google Scholar]

21. Group RC. Dexamethasone in hospitalized patients with Covid-19. *New England Journal of Medicine*. 2021;384(8):693-704. [Full Text]

22. Ibrahim AS, Edwards JEJ, Filler SG. Zygomycosis. 241–251. *Clinical mycology Oxford University Press, New York, NY*. Published online 2003. [PMC]

23. Guinea J, Escribano P, Vena A, et al. Increasing incidence of mucormycosis in a large Spanish hospital from 2007 to 2015: Epidemiology and microbiological characterization of the isolates. *PLoS One*. 2017;12(6):e0179136. [Full Text]

24. Ben-Ami R, Luna M, Lewis RE, Walsh TJ, Kontoyiannis DP. A clinicopathological study of pulmonary mucormycosis in cancer patients: extensive angioinvasion but limited inflammatory response. *Journal of Infection*. 2009;59(2):134-138. [Google Scholar]

25. Howard DH. Acquisition, transport, and storage of iron by pathogenic fungi. *Clin Microbiol Rev*. 1999;12(3):394-404. [Google Scholar]

26. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis transferrin and iron availability. *Diabetes*. 1982;31(12):1109-1114. [Google Scholar]

27. Ibrahim A, Spellberg B, Edwards Jr J. Iron Acquisition: a novel prospective on mucormycosis pathogenesis and treatment. *Curr Opin Infect Dis*. 2008;21(6):620. [Google Scholar]

28. Boelaert JR, de Locht M, Van Cutsem J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. *J Clin Invest*. 1993;91(5):1979-1986. [Google Scholar]

29. Van Cutsem J, Boelaert JR. Effects of deferoxamine, feroxamine and iron on experimental mucormycosis (zygomycosis). *Kidney Int*. 1989;36(6):1061-1068. [Google Scholar]

30. Liu M, Spellberg B, Phan QT, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. *J Clin Invest*. 2010;120(6):1914-1924. [Google Scholar]

31. Bitar D, Van Cauteren D, Lanternier F, et al. Increasing incidence of zygomycosis (mucormycosis), France, 1997–2006. *Emerg Infect Dis*. 2009;15(9):1395. [PMC]

32. Castaldo P, Stratta RJ, Wood RP, et al. Clinical spectrum of fungal infections after orthotopic liver transplantation. *Archives of Surgery*. 1991;126(2):149-156. [PubMed]

33. Da Nam B, Kim TJ, Lee KS, Kim TS, Han J, Chung MJ. Pulmonary mucormycosis: serial morphologic changes on computed tomography correlate with clinical and pathologic findings. *Eur Radiol*. 2018;28(2):788-795. [PubMed]

34. Hammer MM, Madan R, Hatabu H. Pulmonary mucormycosis: radiologic features at presentation and over time. *American Journal of Roentgenology*. 2018;210(4):742-747. [Google Scholar]

35. Singla K, Samra T, Bhatia N. Primary cutaneous mucormycosis in a trauma patient with Morel-Lavallee lesion. *Indian J Crit Care Med*. 2018;22(5):375. [PubMed]

36. Al-Tarrah K, Abdelaty M, Behbahani A, Mokaddas E, Soliman H, Albader A. Cutaneous mucormycosis postcosmetic surgery: a case report and review of the literature. *Medicine*. 2016;95(27). [Google Scholar]

37. Roilides E, Zaoutis TE, Katragkou A, Benjamin Jr DK, Walsh TJ. Zygomycosis in neonates: an uncommon but life-threatening infection. *Am J Perinatol*. 2009;26(8):565. [Google Scholar]

38. Fong KM, Seneviratne EME, McCormack JG. Mucor cerebral abscess associated with intravenous drug abuse. *Aust N Z J Med*. 1990;20(1):74-77. [PubMed]

39. McAdams HP, Rosado de Christenson M, Strollo DC, Patz Jr EF. Pulmonary mucormycosis: radiologic findings in 32 cases. *AJR Am J Roentgenol*. 1997;168(6):1541-1548. [PubMed]

40. Petrikkos G, Skiada A, Sambatakou H, et al. Mucormycosis: ten-year experience at a tertiary-care center in Greece. *European Journal of Clinical Microbiology and Infectious Diseases*. 2003;22(12):753-756. [Google Scholar]

41. Stamm B. Mucormycosis of the stomach in a patient with multiple trauma. *Histopathology*. 2005;47(2):222-223. [PubMed]

42. Teggi A, Fedele A, Bagnato R, Traditi F, Lanzalone CM, De Rosa F. A case of disseminated mucormycosis. *Recenti Prog Med*. 1989;80(6):308-313. [Google Scholar]

43. Nosari A, Oreste P, Montillo M, et al. Mucormycosis in hematologic malignancies: an emerging fungal infection. *Haematologica*. 2000;85(10):1068-1071. [Google Scholar]

44. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KVI. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clinical Infectious Diseases*. 2000;30(6):851-856. [PubMed]

45. 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(12):e405-e421. doi:10.1016/S1473-3099(19)30312-3 [PubMed]

46. Sheth CC, Johnson E, Baker ME, Haynes K, Mühlschlegel FA. Phenotypic identification of Candida albicans by growth on chocolate agar. *Med Mycol*. 2005;43(8):735-738. doi:10.1080/13693780500265998 [Google Scholar]

47. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. *Lancet Infectious Diseases*. 2005;5(10):609-622. doi:10.1016/S1473-3099(05)70238-3 [Google Scholar]

48. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. *Arch Pathol Lab Med*. 2001;125(3):375-378. [Google Scholar]

49. Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebral Mucormycosis : Evolution of the Disease and Treatment Options. 1997;(July). [Google Scholar]

50. Factors S, Mucormycosis R orbital cerebral. MAJOR REVIEW Survival Factors in Rhino-Orbital-Cerebral. 1994;39(1). DOI: 10.1016/s0039-6257(05)80041-4 [PubMed]

51. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J, Ibrahim AS. Recent Advances in the Management of Mucormycosis : From Bench to Bedside. 2009;48(table 1). doi:10.1086/599105 [Google Scholar]

52. Barron MA, Lay M, Madinger NE. 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. 2014;43(4):2012-2014. doi:10.1128/JCM.43.4.2012 [Google Scholar]

53. Sun QN, Fothergill AW, Mccarthy DI, et al. In Vitro Activities of Posaconazole , Itraconazole , Voriconazole , Amphotericin B , and Fluconazole against 37 Clinical Isolates of Zygomycetes In Vitro Activities of Posaconazole , Itraconazole , Voriconazole , Amphotericin B , and Fluconazole against 3. Published online 2002:1581-1583. doi:10.1128/AAC.46.5.1581 [PMC]

54. 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. 2015;50(6):2009-2015. doi:10.1128/AAC.00163-06 [Google Scholar]

55. Dannaoui E, Meis JFGM, Loebenberg D, Verweij PE. Activity of Posaconazole in Treatment of Experimental Disseminated Zygomycosis. 2003;47(11):3647-3650. doi:10.1128/AAC.47.11.3647 [Google Scholar]

56. Ibrahim AS, Spellberg B, Edwards J. Iron acquisition : a novel perspective on mucormycosis pathogenesis and treatment. Published online 2016. doi:10.1097/QCO.0b013e3283165fd1 [Google Scholar]

57. Mignogna MD, Fortuna G, Leuci S, et al. International Journal of Infectious Diseases Mucormycosis in immunocompetent patients : a case-series of patients with maxillary sinus involvement and a critical review of the literature. *International Journal of Infectious Diseases*. 2011;15(8):e533-e540. doi:10.1016/j.ijid.2011.02.005 [PubMed]

58. Fungus B, Unfortunately AB. The outbreak of mucormycosis (the so- called " Black Fungus ") in India is a prime example of the great need for a safer antifungal drug with true fungicidal activity. Published online 2021.

59. Nehara HR, Puri I, Singhal V, IH S, Bishnoi BR, Sirohi P. Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: Case series from the north-western part of India. *Indian J Med Microbiol*. 2021;(December 2020). doi:10.1016/j.ijmmb.2021.05.009 [PubMed]

60. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *Am J Emerg Med*. 2021;42:264-e5. [Google Scholar]

61. Nehara HR, Puri I, Singhal V, IH S, Bishnoi BR, Sirohi P. Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: Case series from the north-western part of India. *Indian J Med Microbiol*. 2021;(December 2020). doi:10.1016/j.ijmmb.2021.05.009 [Google Scholar]

62. Nasir N, Farooqi J, Mahmood SF, Jabeen K. COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: An observational study from Pakistan. *Mycoses*. 2020;63(8):766-770. doi:10.1111/myc.13135 [PubMed]