

Pathophysiology of Mucormycosis

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Abstract: *Mucormycosis is an angio invasive infection that occurs due to the fungi mucorales. It is a rare disease but increasingly recognized in immunocompromised patients. It can be categorized into rhino-orbito-cerebral, cutaneous, disseminated, gastrointestinal, and pulmonary types. Overall increased mortality rate is reported, even though the aggressive treatment is given. The main aim and purpose of this review related to overview and Eopathogenesis of Mucormycosis, fatality of rhinocerebral Mucormycosis, recent advances in diagnostic and treatment methods.*

Background: Mucormycosis is an infection give rise by a group of filamentous molds belong to order Mucorales and class Zygomycetes. Mucormycosis is often known as black fungus disease. This infection mainly targets diabetic and immunocompromised patients. As COVID-19 infection declines the immunity of patients, somucormycosis cases are also increasing due to inhalation of molds containing industrial oxygen.

Objective: The main aim of the present article is to provide a comprehensive review on mucormycosis, its epidemiology, pathophysiology, diagnosis, treatment, and its association with COVID-19.

Methods: We searched the electronic database of PubMed and Google Scholar from inception until May 13, 2021 using keywords. We retrieved all the granular details of case reports/series of patients with mucormycosis, and COVID-19 reported world-wide. Subsequently we analyzed the patient characteristics, associated comorbidities, location of mucormycosis, use of steroids and its outcome in people with COVID-19. An extensive literature search were carried out in various search engine like PubMed, Google Scholars, Research Gate by using the keywords like Mucormycosis, Black fungus, Mucorales, Zygomycetes, Rhizopus, etc. Between period of March, 2021 To June 2021.

Keywords: Mucormycosis, Black Fungus, Mucorales, Diabetes mellitus (DM), COVID, Glucocorticoids, Rhizopus, ROCM

Reference

- [1]. PrakashH, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi 2019; 5:26.
- [2]. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021; 185.
- [3]. AK Gupta ,V. Rhino-orbital Cerebral Mucormycosis. [Updated 2021 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.
- [4]. Mohammadi R, Nazeri M, Sayedayn SM, Ehteram H. A successful treatment of rhinocerebral mucormycosis due to Rhizopus oryzae. Journal of research in medical sciences: The Official Journal of Isfahan University of Medical Sciences, 2014; 19(1): 72.
- [5]. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, Kumar A. COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses 2021 Jun 16.
- [6]. Honavar, Santosh G Code Mucor. Indian Journal of Ophthalmology 2021; 69:1361-1365.
- [7]. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clinical Infectious Diseases, 2005; 41(5): 634-53.
- [8]. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical Manifestationsof mucormycosis. Clinical Infectious Diseases, 2012; 54(suppl_1): S23-34.

- [9]. Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus [Internet]. Vol. 44, Medical Mycology. Med Mycol; 2006 [cited 2021 May 30]. p. 335–42. Available from: <https://pubmed.ncbi.nlm.nih.gov/16772227/>
- [10]. 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/](https://pubmed.ncbi.nlm.nih.gov/24960557/)
- [11]. Bitar D, Lortholary O, Le Strat Y, Nicolau J, Coignard B, Tattevin P, et al. Population-based analysis of invasive fungal infections, France, 2001-2010. Emerg Infect Dis [Internet]. 2014 [cited 2021 May 30];20(7):1149–55. Available from: <https://pubmed.ncbi.nlm.nih.gov/24960557/>
- [12]. Bitar D, Van Cauteren D, Lanternier F, Dannaoui E, Che D, Dromer F, et al. Increasing incidence of zygomycosis (mucormycosis), France, 1997-2006. Emerg Infect Dis [Internet]. 2009 Sep [cited 2021 May 30];15(9):1395–401. Available from: [/pmc/articles/PMC2819884/](https://pubmed.ncbi.nlm.nih.gov/20335060/)
- [13]. Ambrosioni J, Bouchuiguir-Wafa K, Garbino J. Emerging invasive zygomycosis in a tertiary care center: Epidemiology and associated risk factors. Int J Infect Dis [Internet]. 2010 Sep [cited 2021 May 30];14(SUPPL..3). Available from: <https://pubmed.ncbi.nlm.nih.gov/20335060/>
- [14]. Guinea J, Escribano P, Vena A, Muñoz P, Martínez-Jiménez MDC, Padilla B, et al. Increasing incidence of mucormycosis in a large Spanish hospital from 2007 to 2015: Epidemiology and microbiological characterization of the isolates. PLoS One [Internet]. 2017 Jun 1 [cited 2021 May 30];12(6):e0179136. Available from: <https://doi.org/10.1371/journal.pone.0179136>
- [15]. Riley TT, Muzny CA, Swiatlo E, Legendre DP. Breaking the Mold. Ann Pharmacother [Internet]. 2016 Sep 19;50(9):74757. Available from: <http://journals.sagepub.com/doi/10.1177/1060028016655425>
- [16]. Petrikos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54(SUPPL. 1):23–34.
- [17]. 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/>
- [18]. 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](https://pubmed.ncbi.nlm.nih.gov/6818145/)
- [19]. Chinn RYW, 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. Infect Immun [Internet]. 1982 [cited 2021 May 30];38(3):1123–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/6818145/>
- [20]. Ibrahim AS, Kontoyiannis DP. Update on mucormycosis pathogenesis [Internet]. Vol. 26, Current Opinion in Infectious Diseases. Curr Opin Infect Dis; 2013 [cited 2021 May 30]. p. 508–15. Available from: <https://pubmed.ncbi.nlm.nih.gov/24126718/>
- [21]. 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/>
- [22]. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in Human Disease. Clin Microbiol Rev [Internet]. 2000 Apr 1 [cited 2021 May 30];13(2):236–301. Available from: <https://pubmed.ncbi.nlm.nih.gov/10756000/>
- [23]. 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/](https://pubmed.ncbi.nlm.nih.gov/24126718/)
- [24]. Boelaert JR, Fenves AZ, Coburn JW. Deferoxamine Therapy and Mucormycosis in Dialysis Patients: Report of an International Registry. Am J Kidney Dis [Internet]. 1991 [cited 2021 May 30];18(6):660–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/1962650/>

- [25]. De Locht M, Boelaert JR, Schneider YJ. Iron uptake from ferrioxamine and from ferrirrhizoferrin 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/>
- [26]. 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):1914–24. Available from: <https://pubmed.ncbi.nlm.nih.gov/20484814/>
- [27]. Camara-Lemarroy CR, González-Moreno EI, Rodríguez-Gutiérrez R, Rendón-Ramírez EJ, Ayala-Cortés AS, Fraga-Hernández ML, et al. Clinical features and outcome of mucormycosis. *Interdiscip Perspect Infect Dis* [Internet]. 2014 [cited 2021 May 30];2014. Available from: <https://pubmed.ncbi.nlm.nih.gov/25210515/>
- [28]. Trief D, Gray ST, Jakobiec FA, Durand ML, Fay A, Freitag SK, et al. Invasive fungal disease of the sinus and orbit: A comparison between mucormycosis and Aspergillus. *Br J Ophthalmol* [Internet]. 2016 Feb 1 [cited 2021 May 30];100(2):184–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/26112869/>
- [29]. Kim Y Il, Kang HC, Lee HS, Choi JS, Seo KH, Kim YH, et al. Invasive pulmonary mucormycosis with concomitant lung cancer presented with massive hemoptysis by huge pseudoaneurysm of pulmonary artery. *Ann Thorac Surg* [Internet]. 2014 [cited 2021 May 30];98(5):1832–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/25441799/>
- [30]. Neto FMFD, Camargo PCLB, Costa AN, Teixeira RHOB, Carraro RM, Afonso JE, et al. Fungal infection by mucorales order in lung transplantation: 4 case reports. In: *Transplantation Proceedings* [Internet]. Elsevier USA; 2014 [cited 2021 May 30]. p. 1849–51. Available from: <https://pubmed.ncbi.nlm.nih.gov/25131052/>
- [31]. Torres-Narbona M, Guinea J, Martínez-Alarcón J, Muñoz P, Gadea I, Bouza E. Impact of zygomycosis on microbiology workload: A survey study in Spain. *J Clin Microbiol* [Internet]. 2007 Jun [cited 2021 May 30];45(6):2051–3. Available from: <https://pubmed.ncbi.nlm.nih.gov/17392438/>
- [32]. Ingram PR, Suthanathan AE, Rajan R, Pryce TM, Sieunarine K, Gardam DJ, et al. Cutaneous mucormycosis and motor vehicle accidents: Findings from an Australian case series. *Med Mycol* [Internet]. 2014 Oct 27 [cited 2021 May 30];52(8):819–25. Available from: <https://pubmed.ncbi.nlm.nih.gov/25288654/>
- [33]. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Perego C, et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: A case-control observational study of 27 recent cases. *J Infect Dis* [Internet]. 2005 Apr 15 [cited 2021 May 30];191(8):1350–60. Available from: <https://pubmed.ncbi.nlm.nih.gov/15776383/>
- [34]. Ingram CW, Sennesh J, Cooper JN, Perfect JR. Disseminated Zygomycosis: Report Of Four Cases And Review. *Rev Infect Dis* [Internet]. 1989 [cited 2021 May 30];11(5):741–54. Available from: <https://pubmed.ncbi.nlm.nih.gov/2682947/>
- [35]. Rammaert B, Lanternier F, Zahar JR, Dannaoui E, Bougnoux ME, Lecuit M, et al. Healthcare-associated mucormycosis. *Clin Infect Dis* [Internet]. 2012 Feb 1 [cited 2021 May 30];54(SUPPL. 1). Available from: <https://pubmed.ncbi.nlm.nih.gov/22247444/>
- [36]. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). *Clinical Infectious Diseases*, 2012; 54(suppl 1):S55-60.
- [37]. Sciubba JJ, Regezi JA, Rogers RS. PDQ oral disease: diagnosis and treatment. *PMPH-USA*; 2002.
- [38]. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycoses in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. *J. Infect. Dis.*, 2005; 191:1350–60.
- [39]. Spellberg B, Ibrahim A, Rolides E, Lewis RE, Lortholary O, Petrikos G, Kontoyiannis DP, Walsh TJ. Combination therapy for mucormycosis: why, what, and how?. *Clinical infectious diseases*, 2012; 54(suppl 1): S73-8.
- [40]. Skiada A, Lanternier F, Groll AH, Pagano L, Zimmerli S, Herbrecht R, Lortholary O, Petrikos GL. Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). *Haematological*, 2013; 98(4): 492-504.

- [41]. Sipsas N, Gamaletsou M, Anastasopoulou A, Kontoyiannis D. Therapy of mucormycosis. *Journal of Fungi*, 2018; 4(3): 90.
- [42]. L. Pagano, C. G. Valentini, B. Posteraro et al., “Zygomycosis in Italy: a survey of FIMUA-ECMM (Federazione Italiana di Micopatologia Umana ed Animale and European Confederation of Medical Mycology),” *Journal of Chemotherapy*, vol. 21, no. 3, pp.322–329, 2009.
- [43]. Avery RK, Michaels MG. Strategies for safe living after solid organ transplantation external icon. *Am J Transplant*. 2013 Mar;13 Suppl 4:304-10.
- [44]. CDC. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep*. 2000 Oct;49(RR-10):1-125, CE1-7.
- [45]. Davies BW, Smith JM, Hink EM, Durairaj VD. Increased incidence of rhino-orbital-cerebral mucormycosis after Colorado flooding external icon. *Ophthalmic Plast Reconstr Surg*. 2017 May;33(3S Suppl 1):S148-S151.
- [46]. Brizendine KD, Vishin S, Baddley JW. Antifungal prophylaxis in solid organ transplant recipients external icon. *Expert Rev Anti Infect Ther*. 2011 May;9(5):571-81.
- [47]. Rogers TR, Slavin MA, Donnelly JP. Antifungal prophylaxis during treatment for haematological malignancies: are we there yet? external icon *Br J Haematol*. 2011 Jun;153(6):681-97.