Journal of Research in Medical and Dental Science
2021, Volume 9, Issue 11, Page No: 135-141

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

Mucormycosis: The Black Curse of the Ill

Kunika Thakare, Kumar Gaurav Chabra*, Amit Reche, Priyanka Paul Madhu, Alisha Chagani

Department of Public Health Dentistry, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe) Wardha, India

ABSTRACT

Mucormycosis is an angio-invasive infection caused by the Mucorales fungus. Although it is an uncommon condition, it is becoming more common among immunocompromised people. Primary disease is usually caused by an airborne infection that starts in the upper or lower airways and leads to sinusitis, rhino cerebral Mucormycosis, or pulmonary infection. Although infection dissemination to the skin, brain, and other locations is uncommon, direct infection extension to adjacent areas is common if patients do not receive vigorous surgical and medical treatment. Rhino-orbit cerebral, cutaneous, disseminated, gastrointestinal, and pulmonary forms can all be found. Despite the intensive therapy, there is an overall higher death rate. The primary goal and purpose of this study is to provide an overview of Mucormycosis, as well as the diagnostic and therapeutic options.

Key words: Oral Infection, Rhino cerebral mucormycosis, Fungal invasion

HOW TO CITE THIS ARTICLE: Kunika Thakare, Kumar Gaurav Chabra, Amit Reche, Priyanka Paul Madhu, Alisha Chagani, Mucormycosis: The Black Curse of the Ill, J Res Med Dent Sci, 2021, 9(11): 135-141

Corresponding author: Kumar Gaurav Chabra
E-mail ✉ :rajsushil.chhabra@gmail.com
Received: 18/10/2021
Accepted: 03/11/2021

INTRODUCTION

A chronic, subacute, and frequently progressive spectrum of fungal infections from the order of Mucorales from the Zygomycete class is described by the name "mucormycoses" [1]. Mucormycosis is a rare fungal illness that is frequently present in soil, manure, plants, fresh fruit, veggie, air, mould, and even in the healthy individuals. It affects the sinus, brain and lungs and can jeopardise people who are diabetical or have a significant immune defect [2]. The pathologist R. D. Baker from the United States adopted the name "Mucormycosis" for denoting a mycosis of some Mucorales members [3]. The first instance of Mucormycosis was recorded in 1885, by the German doctor Paltauf and characterised as Mycosis Mucorina. N Rhizopus oryzae is the most prevalent organism identified from mucormycosis patients and ~70 percent of all mucormycosis cases is accountable [4].

A large range of opportunistic bacterial and fungal infections have been associated with coronavirus 2019 (COVID-19) caused by severe acute coronavirus-2 (SARS-CoV-2). The predominant fungal pathogens for co-infection in COVID-19 persons have been reported as both Candida and Aspergill [5]. Recently, there have been more and more reports of many occurrences of mucormycosis in patients living with COVID-19 worldwide, especially in India.

Epidemiology

The clinical manifestation of mucormycosis is determined by the underlying medical state of the patient. The most prevalent form of mucormycosis is rhino-orbito-cerebral mucormycosis (44–49%), followed by cutaneous (10–16%), pulmonary (10–11%), disseminated (6–11.6%), and gastrointestinal (2–11%) mucormycosis [6].

Mucormycosis is becoming more prevalent. Because there are few people, there are few population-based studies which differ in capture dates, populations, and defining or diagnostic processes, the actual incidence/prevalence is unknown [7]. Mucormycosis is becoming more prevalent over the world, with an alarming increase in the number of cases reported from developing countries such as India.

Mucormycosis is prevalent in India with a rate of 0.14 instances per 1000 people, which is nearly 80 times higher than the rate in affluent countries [8,9].

Chakrabarti et al. published three successive investigations from a single location in India, finding that the incidence of mucormycosis was 12.9 cases per year in the first decade, 35.6 cases per year over a 5-year period, and 50 cases per year over an eighteen-month period [10].

A single tertiary-care centre in India has documented three successive case series on mucormycosis: 129 cases over ten years (1990–1999), 178 instances over the next five years (2000–2004), and 75 cases over an 18-month period in 2006–2007. Following this, many more Indian centres have reported multiple series of this disease in various risk groups. Three case series on mucormycosis

have been documented in India, including 129 cases over 10 years (1990–1999), 178 cases over the next five years (2000–2004), and 75 cases over an 18-month period in 2006–2007. Following this, multiple series of this disease have been documented in various risk groups in many more Indian centres. The findings show an overall mucormycosis prevalence of 0.14 instances per 1000 people in India, with a prevalence range of 208 177 to 137 807 cases (Mean: 171 504; SD: 12 365.6; 95 percent CI: 195 777–147 688) and a mean of 65 500 (38.2%) related deaths each year [7,11,12].

Clinical manifestations

The mechanism of transmission is reflected in the illness symptoms, with rhinocerebral and pulmonary disorders being the most prevalent. There are other cases of skin, gastrointestinal, and allergy problems. Mucormycosis is divided into rhino-orbito-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal, disseminated, and other miscellaneous forms that include infection of the bones, heart, ear, parotid gland, uterus, urinary bladder, and lymph nodes [13].

Mucorales affects the head and neck in several stages. Infection originates in the palate or paranasal sinuses, spreads to the orbit, and, if not treated promptly, spreads to the brain.

Rhino-orbital-cerebral

Fever, lethargy, headache, orbital pain, sudden loss of vision, ophthalmoplegia, proptosis, ptosis, dilated pupil, corneal anaesthesia and clouding, chemosis, periorbital cellulitis, sinusitis, epistaxis, facial palsy, trigeminal nerve distribution sensory loss, and seizures are some of the signs and symptoms [14,15]. Complications such as cavernous sinus and internal carotid artery thrombosis have also been documented [14–17]. Typically, cerebrospinal fluid findings are non-specific and unremarkable.

Early on, paranasal sinus involvement may appear on computed tomography as benign mucosal thickening. Later, bone destruction occurs. Mucorales enters the retro-orbital area and frontal lobes via the ethmoid or sphenoid sinuses [18,19]. It can also enter the brain via the superior orbital fissure, ophthalmic arteries, the perineural pathway, the cribiform plate, or the carotid artery canal fluid findings are unremarkable as well as nonspecific [20,21].

The typically characterised clinical signal of infection has been black necrotic eschar seen on the palate or nasal mucosa, but this lesion is not always present on presentation of the patient. As a result of infection in the nasal cavity or paranasal sinuses via palatal vessels, involvement of the oral cavity usually manifests as palatal ulceration or necrosis, followed by perforation of the palate.

Ferry et al. observed a black eschar on the skin, nasal mucosa, or palate in 19% (three of 16) of patients at presentation, while the majority (68%) developed this symptom afterwards [15]. Patients with early-stage illness frequently have face cellulitis and anaesthesia, nasal discharge, fever, headache, necrotic turbinates and lethargy [15,16,22–26].

Pulmonary

This is the second most prevalent location of Mucorales infection involvement [27,28]. The major mode of infection is spore inhalation. Its clinical manifestation is identical to that of invasive pulmonary aspergillosis. The radiographic appearance of pulmonary mucormycosis is similar to that of aspergillosis [15,24,29,30]. Both infections have the ability to infiltrate blood arteries and cause thrombosis. Patients with leukaemia have historically been thought to make up the bulk of cases; however, new studies have revealed that diabetes mellitus is the most common underlying illness [31].

Infiltrate, wedge-shaped consolidation, nodule, cavitation, mycetoma, lobar collapse, and, in rare cases, pleural effusion are all radiographic manifestations. The air crescent sign, which generally indicates invasive pulmonary aspergillosis, was present in 12% of the 32 mucormycosis patients evaluated by McAdams et al. On chest radiograph, 66 percent of the mucormycosis cases showed consolidation and 41% had cavitation [32,33].

Cutaneous

Cutaneous mucormycosis can develop as a result of a break in the skin's integrity caused by surgery, burns, contaminated trauma, automobile accidents, abrasions, lacerations, bone fractures, intravenous lines, insect bites, cactus spine injuries, biopsy sites, allergen patch testing, contaminated adhesive tapes, and intramuscular injections.

Cutaneous mucormycosis can present as either a superficial or a deep infection. Pustules, blisters, nodules, necrotic ulcerations, echthyma gangrenosum-like lesions, or necrotizing cellulitis can all occur.

Disseminated mucormycosis affects two or more noncontiguous organs. The majority of individuals with disseminated mucormycosis are neutropenic patients with leukaemia or lymphoma [34,35]. In 23–62 percent of cases of haematological malignancy, dissemination occurs [23,25,35–39]. Organ transplantation, chemotherapy, corticosteroids, and deferoxamine medication are further risk factors for spreading. Many patients are contaminated with several bacteria, viruses, or fungi. Disseminated illness has a near-100 percent mortality rate [16,28,39].

Gastrointestinal

Abdominal discomfort, haematemesis, and melena are common signs and symptoms of gastrointestinal mucormycosis. Given the substantial risk of GI perforation and exanguination, surgical intervention becomes necessary.

Patients with acute myelogenous leukaemia, lymphoma, diabetic ketoacidosis, nonketotic diabetes mellitus,

amoebic colitis, typhoid fever, pellagra, kwashiorkor, malaria, malnutrition, meningococcaemia, and prematurity who have undergone organ, bone marrow, or peripheral blood stem cell transplantation, as well as those with acute myelogenous leukaemia tend to develop gastrointestinal mucormycosis [5,40,41].

Oral manifestations

- Halitosis.
- Redness and swelling of the gums.
- Pus discharge from the gums.
- Loosening of teeth (majorly maxillary teeth).
- Discoloration of the palate usually associated with ulcerations, which may progress into ischemic necrosis and bony denudation in certain cases.
- Headache and pain, usually on one side of the face.
- Swelling seen involving the middle third of the face on the affected side.

Predisposing factors/underlying conditions

Mucorales cause human zygomycosis, which typically develops as an opportunistic infection in immunocompromised hosts. Diabetes, neutropenia, long-term immunosuppressive therapy, chronic prednisone use, iron chelation therapy, broad-spectrum antibiotic use, severe malnutrition, and first breakdown within the integrity of the cutaneous barrier such as trauma, surgical wounds, needle sticks, or burns are all host risk factors.

Diabetes mellitus and ketoacidosis

Diabetes mellitus is the most common underlying illness in mucormycosis patients worldwide. Type II diabetes, which is uncontrolled, is the most frequent. A recent study comparing North and South India discovered diabetic ketoacidosis in 90% of cases from North India and 10% of those from South India. Diabetes has been linked to 73.5 percent of mucormycosis cases in India, 75 percent in Iran, and 72 percent in Mexico [10,13,16,42,43].

Hematological malignancies and hematological somatic cell transplantation

In Europe, the United States, and Australia, the most prevalent underlying disorders in mucormycosis are hematopoietic malignancies (HMs) and hematopoietic somatic cell transplantation (HSCT). In India, HM was a risk factor of 1–9%. When a patient has chronic neutropenia, the risk is increased. HSCT is also a significant risk factor. Mucormycosis incidence ranged from 0.08 percent to 0.69 percent among HSCT recipients. In India, the incidence of HSCT as a risk factor for mucormycosis has been reported to be 1% [22,24,38,44–46].

Solid organ malignancies and solid organ transplantation

Although not as common as HM and HSCT, solid organ malignancies (SOMs) and solid organ transplantation (SOT) are key risk factors for mucormycosis. A prospective, matched case-control research found that renal failure, diabetes, and prior voriconazole and/or caspofungin use were associated with a higher risk of mucormycosis, but tacrolimus, a calcineurin inhibitor, was associated with a lower risk [47].

Corticosteroids and other immunosuppressive medications

Long-term use of corticosteroids and other immunosuppressive agents is a major risk factor for mucormycosis. They're used to treat cancer, organ transplants, and autoimmune illnesses. Corticosteroids inhibit macrophage movement, ingestion, and phagolysosome fusion. They will also cause drug-induced Hyperglycemia. Mucormycosis is associated with long-term (>3 weeks) high-dose systemic corticosteroids. There have been reports of mucormycosis associated with short doses of corticosteroids [48,49].

Iron overload

Because iron is crucial in the pathophysiology of mucormycosis, elevated serum iron levels may be a risk factor. Iron is typically bound to transferrin and ferritin and is therefore unavailable to Mucorales fungi. The affinity of those proteins to bind iron is diminished in patients with diabetic ketoacidosis or other types of acidosis [50,51].

Breakthrough mucormycosis

The use of antifungal prophylaxis or medication that is effective against Aspergillus but not Mucorales (voriconazole and echinocandins) is another factor that will predispose to mucormycosis [23,52–54].

In condition where there is no underlying disease

In such situations, trauma or burns are the most common predisposing factors, resulting to cutaneous disease. Trauma can be minor (injection sites, animal bites, gardening, etc.) or severe, such as an automobile accident, natural disasters, or surgery. Mucormycosis has also been documented as a result of a combat-related injury.

Healthcare-associated mucormycosis

There have been numerous reports of healthcare-associated mucormycosis, either as single cases or as outbreaks. During an eighteen-month period, 75 cases of mucormycosis were published in an Indian magazine, with 9 percent being nosocomial.

- The most common cause of infection is the use of non-sterile items. Bandages, adhesives, nitro-glycerine patches, contaminated linen, wooden tongue depressors, ostomy bags, and probiotics have

all been implicated. There has even been a report of an epidemic caused by allopurinol tablets and packed food.

- Various treatments and medical devices, such as catheters, insulin pumps, and finger sticks, as well as tube insertion, teeth extractions, and surgery.
- Environmental factors can potentially be a source of illness [3,55–59].

DIAGNOSIS

Clinical diagnosis

The Smith et al. [60] for the clinical diagnosis of mucormycosis, developed in 1950, is currently regarded the gold standard and include the following:

- Black, necrotic turbinate's that are easily confused with dried, crusted blood.
- Blood-tinged nasal discharge and face pain on the same side.
- Soft peri-orbital or peri-nasal edema with colouring and induration.
- Ptosis of the eyelid, proptosis of the eyeball, and complete ophthalmoplegia.
- Multiple cranial nerve palsies unrelated to recorded lesions.

Laboratory diagnosis and cultures

Mucormycosis diagnosis entails a careful examination of clinical manifestations, resonance imaging modalities, the use of computerized tomography (CT) in the early stages, expert evaluation of cytological and histological provision, the best application of clinical microbiological technique, and the execution of molecular detection. The detection of host variables greatly contributes to the calculation of a patient's risk of invasive mucormycosis. The various laboratory procedures for detecting mucor include PAS stains, interrogation, calcofluor, histological investigation, Gomori methenamine silver stain, culture, molecular approaches, and fluorescent in situ hybridization. Kontoyiannis et al. had described in a study that, a fundamental challenge in the detection of mucormycosis is its indefinable clinical presentation and repeated occult distribution, necessitating the use of a sensitive nonculture-based investigative method. The tissue-based analysis is the gold standard analytic technique for confirmation. Mucormycosis frequently presents as an intrusive image of perforation into bone regions. There have been reports of oroantral communication or perforation spreading to face tissues. Confirmation of clinical diagnosis necessitates microscopic analysis of biopsied tissue. Histopathological examination of the tissue reveals broad, non-septate hyphae with pathognomonic hyphae branching at right angles. The hyphae will be seen with a deeper connective tissue invasion. The particular staining procedure, Grocott-Gomori methylamine silver stain, will aid in the identification of non-septate hyphae. During histological analysis, cases with bony perforations may show the presence of fungal pathogens in marrow areas. It is worth mentioning that cytological specimens obtained from cases with a histological diagnosis of mucormycosis may be devoid of organisms in fungal culture. A thorough clinical examination of the oral cavity in invasive lesions is recommended to achieve a clinical diagnosis, because not all cases of mucormycosis will show the classical diagnostic interpretation in imaging studies such as radiographs, computerised tomography (CT), magnetic resonance (MR), culture studies, or serological tests [23,34,61].

Differential diagnosis

It includes maxillary sinus aspergillosis, maxillary sinus neoplasia, soft tissue radio necrosis, soft tissue infarction and other deep fungal infections.

TREATMENT

Multiple therapies, either at the same time or at different times and intensities, are used to treat mucormycosis. The most important concepts of mucormycosis treatment are risk stratification for disease severity and aggressive clinical and laboratory diagnosis. Mucormycosis is treated using a combination of therapies, which can be utilised at the same time or at different times and intensities. Mucormycosis treatment revolves around risk stratification based on disease severity and aggressive clinical and laboratory diagnosis.

Antifungal Agents for mucormycosis

Amphotericin B lipid formulations

Amphotericin B (AMB) is the medicine of choice for the primary treatment of mucormycosis. AMB's effectiveness has been demonstrated in both lab (in vitro and in vivo) and clinical investigations. The ideal dosage for AMB and its formulations against mucormycosis is unknown, as it is for many antifungal drugs and mycoses. According to current guidelines, a good daily dose of LAMB and ABLC is 5 mg/kg/day. AMB's in vitro action against Mucorales varies greatly [62–64].

Triazoles

Triazoles work by reducing the amount of ergosterol in the fungal cell wall. Fluconazole, itraconazole, and voriconazole are triazole antifungals that have minimal or no effect against Mucorales [65].

Isavuconazole

Isavuconazole is the physiologically active form of the prodrug isavuconazonium sulphate and could be a novel broad-spectrum triazole. It comes in intravenous and oral forms, and it's given at a loading dose of 200 mg three times a day for two days, then 200 mg every day after that.

Despite the lack of good clinical data, the use of a combination of antifungals to treat mucormycosis in immunocompromised patients has grown more widespread. The benefits of such a therapeutic approach

include synergistic effects and larger coverage, while the drawbacks include probable antagonistic effects, drug interactions, toxicity, and cost. The combination of AMB +echinocandin was successful in 6 of 7 diabetic individuals with rhino-orbital or rhino-cerebral mucormycosis, compared to just 7 of 22 patients treated with ABLC alone (p=0.02). Data on the efficacy of combining AMB with a triazole in the treatment of mucormycosis are limited [52,57,58,66,67].

Surgery

The heart of mucormycosis treatment is surgical excision of necrotic tissues. Surgery combined with proper systemic antifungal therapy has been demonstrated to increase survival in pulmonary mucormycosis patients compared to antifungal therapy alone. In patients with early, circumscribed illness or major medical comorbidities, endoscopic surgery is favoured to open surgery. For significant disease, open operations such as maxillectomy, ocular exenteration, and/or craniofacial resection are favoured; nevertheless, no survival benefit has been demonstrated for such a dramatic treatment, especially in patients with limited expectation [62,68,69].

Adjunctive therapy

Along with surgery and appropriate early antifungal agents, reversing immunosuppression is a critical component of mucormycosis therapy. The majority of patients who die from this disease have poor bone marrow recovery or require long-term immunosuppressive therapy (such as those with GVHD). As a result, any attempt to reverse neutropenia in haematology patients should be made, either through the use of hematopoietic growth factors or, in rare cases, through leukocyte transfusions. For patients with uncontrolled diabetes and/or ketoacidosis, aggressive glycaemic control is critical. Iron chelators, which reduce available iron and thus inhibit iron absorption, were proposed as a possible adjunctive therapy by researchers [70,71].

OVERVIEW

In a recent estimate for the year 2019–2020, mucormycosis prevalence ranged from 0.005 to 1.7 per million people worldwide, with India's prevalence approximately 80 times higher (0.14 per 1000) than developed countries. In other words, India has the world's highest rate of mucormycosis. Despite this, India has the world's second-largest diabetes mellitus (DM) population and was the world's diabetes capital until recently. Importantly, in India, diabetes mellitus is the most prevalent risk factor for mucormycosis, whereas in Europe and the United States, haematological malignancies and organ transplant take the lead.

Early detection and treatment can lessen the need for significant surgery and consequent deformity, as well as enhance survival.

Clinicians should be aware of the risk of mucormycosis in patients recovering from COVID-19, particularly those who are receiving improper steroid therapy or have uncontrolled diabetes. When treating COVID-19 patients, a strong index of suspicion should be maintained since mucormycosis, unlike COVID-19, is possibly curable if detected early. There's also a need to be concerned about steroid use in a responsible manner. There is also a requirement to be concerned about the prudent use of steroids. It may be prudent to avoid steroid and immunosuppressive use for COVID-19 when there is no oxygen requirement and no evidence of a florid inflammatory response. Antibacterial use that is too early or too aggressive can also be harmful. The key to managing mucormycosis is early diagnosis and the initiation of appropriate antifungal treatment, as well as timely surgical intervention if necessary. Because mucormycosis is an uncommon disease characterised by variability of hosts and sites of infection, as well as the multitude of offending Mucorales, it is difficult to obtain reliable data for its treatment. As a result, no prospective, randomised clinical research exists.

REFERENCES

1. Kwon-Chung KJ. Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. Clin Infect Dis Off Publ Infect Dis Soc Am 2012; 54:8-15.
2. Lewis RE, Kontoyiannis DP. Epidemiology and treatment of mucormycosis. Future Microbio 2013; 8:1163-75.
3. Petrikkos G, Skiada A, Lortholary, O et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 2012; 54:S23-34.
4. Suganya R, Malathi N, Karthikeyan V, et al. Mucormycosis: A brief review. J Pure Appl Microbiol 2019; 13:161-5.
5. Al-Tawfiq JA, Alhumaid S, Alshukairi AN, et al. COVID-19 and mucormycosis superinfection: the perfect storm. Infection 2021; 1-21.
6. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metabolic Syndrome Clin Res Rev 2021.
7. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. Clin Microbio Inf 2019; 25:26-34.
8. Patel A, Patel S, Fulzele P, et al. Quarantine an effective mode for control of the spread of COVID19? A review. J Fam Med Prim Care 2020; 9:3867–71.
9. Srivastava KC, Shrivastava D, Chhabra KG, et al. Facade of media and social media during covid-19: A review. Int J Res Pharm Sci 2020; 142–9.

10. Chander J, Kaur M, Singla N, et al. Mucormycosis: Battle with the Deadly Enemy over a Five-Year Period in India. J Fungi 2018; 4:46.
11. Mohod S, Nemade SS, Goenka YS, et al. COVID-19: A systematic approach to solve the dilemma. Int J Res Pharm Sci 2020; 1334–8.
12. Mandwar S, Dharampuria S, Nimbulkar G, et al. Misconceptions and myths about COVID-19. Int J Res Pharm Sci 2020; 1319–22.
13. Solano T, Atkins B, Tambosis E, et al. Disseminated mucormycosis due to Saksenaea vasiformis in an immunocompetent adult. Clin Infect Dis Off Publ Infect Dis Soc Am 2000; 30:942–3.
14. Wall SJ, Lee KH, Alvarez JD, et al. Quiz Case 1. Arch Otolaryngol Neck Surg 2000; 126:236–236.
15. Tedder M, Spratt JA, Anstadt MP, et al. Pulmonary mucormycosis: Results of medical and surgical therapy. Ann Thorac Surg 1994; 57:1044–50.
16. Chakrabarti A, Das A, Sharma A, et al. Ten years' experience in zygomycosis at a tertiary care centre in India. J Infect 2001; 42:261–6.
17. Chakrabarti A, Singh R. Mucormycosis in India: Unique features. Mycoses 2014; 57:85–90.
18. Andrews M, David R, Allan F, et al. Tracheal mucormycosis. Ann Thorac Surg 1997; 63:230–232.
19. Artis WM, Fountain JA, Delcher HK, et al. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis transferrin and iron availability. Diabetes 1982; 31:1109–1114.
20. Alvarez OA, Maples JA, Tio FO, et al. Severe diarrhea due to Cokeromyces recurvatus in a bone marrow transplant recipient. Am J Gastroenterol 1995; 90:1350–1.
21. Andrade ZA, Paula LA, Sherlock ÍA, et al. Nasal granuloma caused by entomophthora coronata. Am J Trop Med Hyg 1967; 16:31–3.
22. Funada H, Matsuda T. Pulmonary mucormycosis in a hematology ward. Intern Med Tokyo Jpn 1996; 35:540–544.
23. Kontoyiannis DP, Wessel VC, Bodey GP, et al. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis Off Publ Infect Dis Soc Am 2000; 30:851–856.
24. Lee FY, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. Arch Intern Med 1999; 159:1301–1309.
25. Meyer RD, Rosen P, Armstrong D. Phycomycosis complicating leukemia and lymphoma. Ann Intern Med 1972; 77:871–879.
26. Baddley JW, Stroud TP, Salzman D, et al. Invasive mold infections in allogeneic bone marrow transplant recipients. Clin Infect Dis 2001; 32:1319–1324.
27. Parfrey NA. Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. Medicine 1986; 65:113–123.
28. Lehrer RI, Howard DH, Sypherd PS, et al. Mucormycosis. Ann Intern Med 1980; 93):93–108.
29. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000; 13:236–301.
30. Bigby TD, Serota ML, Tierney LM, et al. Clinical spectrum of pulmonary mucormycosis. Chest 1986; 89:435–439.
31. Espinel-Ingroff A, Oakley LA, Kerkering TM. Opportunistic zygomycotic infections. A literature review. Mycopathologia 1987; 97:33–41.
32. McAdams HP, Rosado de Christenson M, Strollo DC, et al. Pulmonary mucormycosis: radiologic findings in 32 cases. AJR Am J Roentgenol 1997; 168:1541–1548.
33. Record NB Jr, Ginder DR. Pulmonary phycomycosis without obvious predisposing factors. JAMA 1976; 235:1256–7.
34. Nolan RL, Carter RR, Griffith JE, et al. Subacute disseminated mucormycosis in a diabetic male. Am J Med Sci 1989; 298:252–255.
35. Nosari A, Oreste P, Montillo M, et al. Mucormycosis in hematologic malignancies: an emerging fungal infection. Haematologica 2000; 85:1068–71.
36. Eucker J, Sezer O, Lehmann R, et al. Disseminated mucormycosis caused by Absidia corymbifera leading to cerebral vasculitis. Infection 2000; 28:246–50.
37. Ibrahim AS, Spellberg B, Walsh TJ, et al. Pathogenesis of mucormycosis. Clin Infect Dis Off Publ Infect Dis Soc Am 2012; 54:S16–22.
38. Morrison VA, McGlave PB. Mucormycosis in the BMT population. Bone Marrow Transplant 1993; 11:383–388.
39. Pagano L, Ricci P, Tonso A, Nosari A, et al. Mucormycosis in patients with haematological malignancies: a retrospective clinical study of 37 cases. GIMEMA Infection Program. Br J Haematol 1997; 99:331–336.
40. Parra R, Arnau E, Julia A, et al Survival after intestinal mucormycosis in acute myelogenous leukemia. Cancer 1986; 58:2717–2719.
41. Vera A, Hubscher SG, McMaster P, et al. Invasive gastrointestinal zygomycosis in a liver transplant recipient: Case report. Transplantation 2002; 73:145–7.
42. Al-Rikabi AC, Al-Dohayan AD, Al-Boukai AA. Invasive mucormycosis in benign gastric ulcer. Saudi Med J 2000; 21:287–90.
43. Ko WJ, Chien NC, Chou NK, et al. Infection in heart transplant recipients: Seven years' experience at

the national Taiwan university hospital. Transplant Proc 2000; 32:2392–2395.

44. Grossi P, Farina C, Fiocchi R, et al. Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients: A multicenter retrospective study. Transplantation 2000; 70:112–116.
45. Talmi YP, Goldschmied-Reouven A, Bakon M, et al. Rhino-orbital and rhino-orbito-cerebral mucormycosis. J Am Acad Otolaryngol Head Neck Surg 2002; 127:22–31.
46. Latif S, Saffarian N, Bellovich K, et al. Pulmonary mucormycosis in diabetic renal allograft recipients. Am J Kidney Dis Off J Natl Kidney Found 1997; 29:461–464.
47. Sugar AM. Mucormycosis. Clin Infect Dis 1992; 14:S126–S129.
48. Hocqueloux L, Bruneel F, Pages CL, et al. Fatal invasive aspergillosis complicating severe Plasmodium falciparum malaria. Clin Infect Dis Off Publ Infect Dis Soc Am 2000; 30:940–2.
49. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: Emphasis on perineural invasion and fungal morphology. Arch Pathol Lab Med 2001; 125:375–378.
50. Stefani FH, Mehraein P. Acute rhino-orbito-cerebral mucormycosis. Ophthalmol J Int Ophtalmol Int J Ophthalmol Z Augenheilkd 1976; 172:38–44.
51. Kalayjian RC, Herzig RH, Cohen AM, et al. Thrombosis of the aorta caused by mucormycosis. South Med J 1988; 81:1180–2.
52. Lamaris GA, Ben-Ami R, Lewis RE, et al. Increased virulence of zygomycetes organisms following exposure to voriconazole: A Study involving fly and murine models of zygomycosis. J Infect Dis 2009; 199:1399–406.
53. Siwek GT, Dodgson KJ, de Margarida MS, et al. Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. Clin Infect Dis 2004; 39:584–7.
54. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem. Cell Transplants 2009.
55. Duffy J, Harris J, Gade L, et al. Mucormycosis outbreak associated with hospital linens. Pediatr Infect Dis J 2014; 33:472–6.
56. LeMaile-Williams M, Burwell LA, Salisbury D, et al. Outbreak of cutaneous rhizopus arrhizus infection associated with karaya ostomy bags. Clin Infect Dis 2006; 43:e83–8.
57. Cheng VCC, Chan JFW, Ngan AHY, et al. Outbreak of intestinal infection due to rhizopus microsporus. J Clin Microbiol 2009; 47:2834–2843.
58. Hampson FG, Ridgway EJ, Feeley K, et al. A fatal case of disseminated zygomycosis associated with the use of blood glucose self-monitoring equipment. J Infect 2005; 51:269–272.
59. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: A review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 2004; 10:31–47.
60. Ishimitsu R, Urabe S, Kataoka S, et al. Invasive aspergillosis of the maxillary sinus. Pract Otorhinolaryngol 1998; 91:915–918.
61. Chakrabarti A, Singh R. Mucormycosis in India: unique features. Mycoses 2014; 57:85–90.
62. Dolatabadi S, Ahmadi B, Rezaei-Matehkolaei A, et al. Mucormycosis in Iran: A six-year retrospective experience. J Mycol Médicale 2018; 28:269–273.
63. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi 2019; 5:26.
64. Vaezi A, Moazeni M, Rahimi MT, et al. Mucormycosis in Iran: A systematic review. Mycoses 2016; 59:402–415.
65. Stemler J, Hamed K, Salmanton-García J, et al. Mucormycosis in the middle East and North Africa: Analysis of the Fungi Scope® registry and cases from the literature. Mycoses 2020; 63:1060–1068.
66. Prabhu S, Alqahtani M, Al Shehabi M. A fatal case of rhinocerebral mucormycosis of the jaw after dental extractions and review of literature. J Infect Public Health 2018; 11:301–303.
67. Walsh TJ, Gamaletsou MN, McGinnis MR, et al. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis 2012; 54:S55–60.
68. McDermott NE, Barrett J, Hipp J, et al. Successful treatment of periodontal mucormycosis: report of a case and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2010; 109:e64–9.
69. Gollard R, Rabb C, Larsen R, et al. Isolated cerebral mucormycosis: case report and therapeutic considerations. Neurosurg 1994; 34:174–177.
70. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: A clinical and diagnostic perspective from China. Mycopathol 2020; 1–8.
71. Jensen HE, Salonen J, Ekfors TO. The use of immunohistochemistry to improve sensitivity and specificity in the diagnosis of systemic mycoses in patients with haematological malignancies. J Pathol 1997; 181:100–105.