DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

A Comprehensive Review on Mucormycosis as co infection of Immunodeficiency Diseases

Najwan Abbas Mohammed, Biotechnology Department, College of Science, University of Diyala, 32001, Iraq.
Email: najwanabbas@uodiyala.edu.iq

Abstract

Mucormycosis is a fatal, life-threatening fungal infection occurring in humans that is associated with considerable morbidity and mortality. It is caused by a group of ubiquitous saprophytic molds, which typically affect patients with weak immune defences such as diabetes mellitus, diabetic ketoacidosis, malignant hematological diseases, post-hematopoietic stem cell or solid organ transplants, as well as those with neutropenia. Mucormycosis is mostly related to the current COVID-19 epidemic and the overuse of steroids but can also be caused by haemato-oncological conditions and other health conditions, such as unbalanced diabetes or caustic injuries. It mostly impacts the nose and sinuses, affecting the eyes and other parts of the body. Immediate treatment of mucormycosis is required, consisting of reversal of underlying risk factors, prompt antifungal therapy (preferably as lipid formulations of amphotericin B or isavuconazole), and early surgical debridement. However, the stringent neutropenic and metabolic status of these patients prevents early diagnosis and withholds aggressive antifungal and surgical treatments. The ability of mucormycosis to invade blood vessels and cause angioinvasion, thrombosis, tissue infarction, and the formation of fungal emboli, increases mortality among patients. New surveillance strategies, novel preventive strategies, new applicative detection techniques, novel antifungal agents, or screening for effective agent repurposing are immediately needed to pave the way to enhance the survival of these high-risk patient populations from this deadly infection and reduce the global burden. The present review aimed to provide an exhaustive overview of mucormycosis, including basic information, etiology, epidemiology and incidence, pathogenesis, risk factors, clinical manifestations, diagnosis modalities, and treatment.

Keywords: *Mucormycosis, Mucorales, Rhizopus, epidemiology, Diabetes.*

1. Introduction

Mucormycosis is a rare but deadly fungal infection. It is caused by filamentous fungi belonging to the order Mucorales including *Rhizopus, Mucor, Rhizomucor, Absidia*, and other genera of *Cunninghamella*, among others [1]. Mucormycosis is not a recent illness; rather, it has long existed but was not well-known. Although it is an unusual angio-obtrusive illness, we cannot rationalize it as a recently formed [2], but one primary cause of the recent cases of mucormycosis is the COVID-19 infection [3].

Mucormycosis is a severe fungal infection caused by mucormycetes molds, that has five main clinical forms, which are gastrointestinal, rhinocerebral, pulmonary, cutaneous, and disseminated, and the rare form, miscellaneous form. Although mucormycosis is rare, it has become a concern to healthcare providers due to the increase in cases following COVID-19, substantially influencing the

DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

number of cases and the severity of the disease. This has led to the "COVID-19 associated mucormycosis (CAM)" terminology. The association between anxiety, depression, and post-COVID-19 mucormycosis has been studied, demonstrating that during the course of their illness, patients experienced significant psychological distress [4].

CAM presents multiple challenges in treatment, including resistance to antifungals, delayed diagnosis, and the difficulty in simultaneous treatment of COVID-19 related co-morbidities. Early recognition and effective management of patients with CAM are essential. Generally, the first line of treatment includes Amphotericin B and surgical debridement. However, due to the limitations of these treatments, healthcare providers and researchers are exploring alternative treatments and adjunct therapy in an effort to improve treatment outcomes and patient prognosis [5]. The present review aimed to provide an exhaustive overview of mucormycosis, including basic information, etiology, epidemiology and incidence, pathogenesis, risk factors, clinical manifestations, diagnosis modalities, and treatment.

2. Epidemiology and Incidence

Despite major advancements in the treatment of immunocompromised hosts, the incidence of mucormycosis has increased over recent decades owing to the increasing number of organ transplant and cancer, diabetic patients, and other emerging risk factors, new diagnostic tools allowing early diagnosis, and the existence of a highly susceptible population [6]. In several large epidemiological studies reported between 1935 and 1964, widespread geographic variation in the incidence of mucormycosis was reported, with a high incidence in India and Austria, today, with the advent of modern diagnostic modalities and the ability to isolate and characterize the offending organisms beyond the genus level, more cases are being reported from all over the world [7].

Studies conducted in Europe, India, and Brazil confirm the widespread geographic distribution of the disease, Mucormycosis, as a complication in patients with poorly controlled diabetes, has a particular predilection for the Indian subcontinent. The rhinocerebral form seems to be the most common variant of the disease in the Indian subcontinent, whereas in Western countries, pulmonary mucormycosis seems to be more common [8]. In Iraq-Basrah, there were 84.3% of affected patients were immuno-compromised, and the main single risk factor was diabetes mellitus with 44.4% of the study group [9], in addition to that the majority of mucormycosis infections were observed in patients with cancers [10].

The incidence rate of mucormycosis among female patients undergoing gastric bypass surgery is significantly higher than that for females in the general population or for males undergoing gastric bypass surgery. The incidence of mucormycosis is higher among kidney transplant patients than for other solid organ transplants. In other transplant patients, central nervous system mucormycosis may present differently than in other patient populations [11]. The incidence of mucormycosis was low until the late 1990s. However, thereafter, the rates began to increase. In 2006, it had an incidence of approximately 1.7 per 1,000,000 patients per year. Additionally, The incidence of mucormycosis cases remained relatively stable from 2006 to the end of the study period in 2015 [12]. The 1-year relative survival of mucormycosis appears to have increased for all years after 2009, but the ranges have wide confidence intervals, which makes the analysis more uncertain [13]. The 5-year relative survival of mucormycosis has declined modestly for all years since 2004. The 1-year mortality rate of

DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

mucormycosis is close to 70%. The 5-year mortality rate of mucormycosis has been upward of 80% for most years since 2005 [14].

3. Pathogenesis

The mode through which a patient might contract the black fungus involves sporangiospores entering through ingestion, inhalation, or through cuts or injuries. In addition, they can enter the body through medical devices, a lack of proper ventilation, or the use of oxygen concentrators that are not overcrowded [15]. One of the main features of mucormycosis is tissue necrosis, which presents itself frequently and can often necessitate significant and repetitive debridement procedures. Dissemination occurs in roughly one-third of mucormycosis cases. The angioinvasive nature of the fungus may cause extensive local infections that cause damage to the respiratory, cerebral, and gastrointestinal vascular systems [16].

The pathogenesis of mucormycosis is multifactorial and involves the filamentous growth of the fungus, iron uptake, and its ability to induce angioinvasion and tissue necrosis. Mucorales produce similar types of extracellular proteolytic enzymes. Some extracellular enzymes such as acid and alkaline proteinases, elastase, laminate, phospholipases, and phospholase B have been documented in different genera of Mucorales which could break down the structural components of human body tissues to facilitate tissue invasion by Mucorales. Take, for example, Rhizopus elastase (RE) could impair the phagocytic function of neutrophils and induce neutrophil apoptosis by degrading the elastin of the host tissue [17]. Protein kinase C (PKC) is a family of protein kinases that are activated by increased intracellular Ca2+ and diacylglycerol. PKC activates NADPH oxidase in phagocytic cells to generate reactive oxygen species (ROS) that kill phagocytosed organisms. RE may diminish the ability of neutrophils to kill *Rhizopus*/Mucorales spores by down-regulating the signaling channel of PKC, inhibiting the ROS burst, and enhancing the phagocytosis of spores. Mucorales can produce several metalloproteinases and their substrates are found to be on the surface of endothelial cells, suggesting that these enzymes may candidly digest the protein components on the endothelial surface [18].

Furthermore, the innate immune system cells, including monocytes, macrophages, neutrophils, natural killer cells, and platelets, play a critical role in dealing with fungal infections. Mucorales employ various strategies to evade innate immunity: iron assimilation (high affinity iron permeases), escape from macrophage killing with phospholipases, enhanced resistance to neutrophil-pseudohypha-mediated destruction (as do *C. albicans*), and prevention of defensin- or calprotectins-mediated killing. Mucorales secrete proteases to destroy platelets, to efface immune surveillance, and to adhere endothelium (further use fibrin and other matrix elements to generate new hyphae) and then penetrate tissues [19]. At any of these steps, the innate immunity could block fungal growth and limit the infection. Only a few drugs are able to affect the metabolism of different fungal cells. Stimulation of protective pro-inflammatory Th17 response significantly improves the prognosis of mucormycosis. These results are reliable proof of the effectiveness of the immune response in host protection against Mucorales [20].

The etiology of mucormycosis is significantly influenced by iron metabolism [21]. Mucormycosis can perform a variety of enzymatic functions in addition to obtaining iron from the host for life and growth. When *Rhizopus oryzae* was used to assess iron sequester activity, it was shown that mucormycosis grew extremely slowly in serum without iron but quickly in a medium with iron [22].

DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

According to studies, some iron chelators function as siderophores by transferring iron to fungal cells to promote their growth, while others act as inhibitors of *Rhizopus* growth by capturing free iron. As a result, patients receiving iron treatments, such as deferoxamine for iron overload, are more likely to contract mucormycosis [23].

4. Risk Factors

The development of mucormycosis has been associated with various risk factors, as shown in Fig. 1. The classical risk factors for mucormycosis include poorly controlled diabetes mellitus, iron overload, and profound and prolonged neutropenia. Reports over the last few decades suggest that other clinical risk factors are emerging, including the use of corticosteroids, previous voriconazole prophylactic therapy, and the presence of trauma [24].

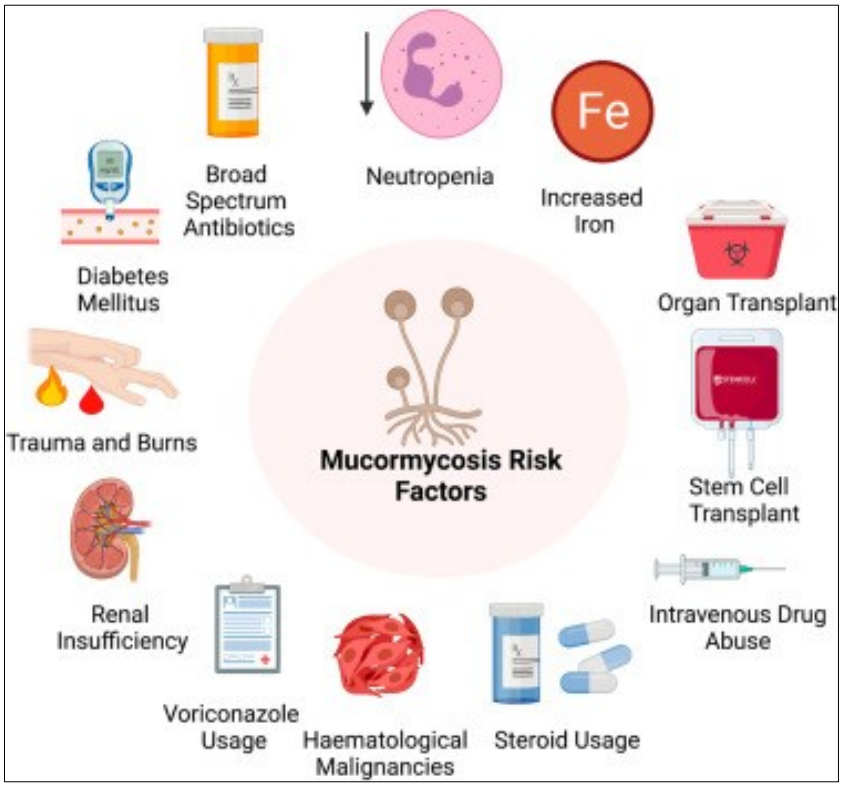

Fig. 1. Risk factors involved in mucormycosis development

Physical damage or trauma may involve patients with open wounds from traumatic injuries or burns, patients with soft-tissue wounds, patients with severe lacerations, particularly with the presence of metal or other foreign materials, and post-surgical intra-abdominal wounds. Other risk factors concern malnutrition, primarily among females related to gastric bypass surgery, and chronic liver or renal disease [25]. Patients with various types of iron overload have an increased risk for mucormycosis. In one study, one-third of patients had known iron overload at the time of their mucormycosis infection, which is usually related to deferoxamine treatment for thalassemia or myeloproliferative disease. Iron overload associated with transfusion of packed red blood cells and iron-chelation therapy for sickle cell anemia, aplastic anemia, myelodysplasia, or other conditions also may contribute to the susceptibility [26].

DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

Diabetes mellitus is the most common risk factor for rhinomaxillary and rhinocerebral mucormycosis, but managing patients with uncontrolled diabetes is a significant challenge. Patients with hematologic malignancies and neutropenia have an increased risk for pulmonary mucormycosis, and those with burns or soft tissue injury are at risk for cutaneous mucormycosis [27,9]. Diabetic ketoacidosis, usually occurring in a patient who has not previously been known to have diabetes mellitus, forms a very recognizable subgroup. This may be associated with or complicated by pancreatitis. Severe neutropenia is found in many patients and usually represents the progression of the neutropenia induced by a cytotoxic regimen antecedent to a diagnosis of leukemia or a similar hematological condition [28]. Mucormycosis is more common in hematological malignancies and in recipients of bone and solid organ cell transplants than diabetic subjects [29].

Additionally, prolonged neutropenia, mitotic chemotherapy, graft-versus-host-disease, prolonged use of corticosteroids, along with broad-spectrum antimicrobial agents, such as limited brilliant complex of therapeutic dimethyl (DMP) to invasive treatment, and specific alpha-delta drugs (interaction facility cancimen therapy) or the delay in providing interferon-gamma-1b (IFN-gamma 1-inn) therapy to pharmacological or therapeutic neupogen are the other most common underlying conditions [30].

5. Clinical Manifestations

There are six different mucormycosis types based on the anatomical regions involved including "rhino-orbito-cerebral, pure pulmonary, cutaneous and subcutaneous, disseminated, gastrointestinal involvement, and other rare forms, like liver, joint, endocardium, and cardiovascular mucormycosis" Table (1).

Table 1: Types of Mucormycosis

References	Types of mucormycosis	Atypical risk factors	Percentage
[31, 32]	Rhino-orbital-cerebral	Diabetes mellitus, Malignancy, and organ transplant	25-39%
[33,34]	Pulmonary	neutropenia, lung transplantation, and chemotherapy	24-30%
[35]	Cutaneous/ soft tissue	Trauma and burns	19-26%
[36]	Disseminated	Iron overload	15-23%
[37,38]	Gastrointestinal	uncontrolled diabetes, immunosuppression, premature birth, and malnutrition	2-11%
[39]	Miscellaneous (bone or joints, heart, and peritoneum)	immunosuppressed individuals, infected medical equipment (catheters, sticky tapes), and traumatic injections during surgery	Rare

DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

6. Diagnostic Modalities and Challenges

The diagnostic techniques for mucormycosis include determining clinical features, early-stage "use of computed tomography (CT), magnetic resonance imaging modalities, expert evaluation of histological and cytological provision, best use of clinical microbiological technique, and molecular detection." When assessing a patient's risk of developing invasive mucormycosis, host factor identification is crucial. Direct investigation, calcofluor, "Periodic acid-Schiff (PAS)" stains, histological analysis, "Gomori methenamine silver stain", culture, molecular techniques, and fluorescence in situ hybridization are among the laboratory methods for identifying mucor [40].

Simple computed tomography of the thorax is utilized to diagnose pulmonary mucormycosis, while magnetic resonance imaging of the paranasal sinuses and a cerebral contrast study are the radiological tests employed for the diagnosis of rhino orbital-cerebral mucormycosis. A biopsy of the afflicted tissues is critical for the histopathological diagnosis of mucormycosis. To confirm the infection, tissue sections stained with Hematoxylin-eosin (HE), Grocott-Gomori methenamine-silver (GMS), Periodic acid-Schiff (PAS), or both may show tissue penetration of unseparated hyphae. Giemsa staining and fresh or calcofluor white may be used for microscopic investigation, which is crucial for the early identification of mucormycosis [41].

7. Treatment and Management

Mucormycosis is treated by early detection, fast antifungal medication, surgical debridement, and the elimination of underlying predisposing risk factors [42]. Amphotericin B is considered the first-line therapy for mucormycosis, as it has broad-spectrum activity against various fungi, including Mucorales species. However, due to its nephrotoxicity and other side effects, lipid formulations of amphotericin B, such as liposomal amphotericin B, are often preferred for mucormycosis treatment . In cases of intolerance or resistance to amphotericin B, other antifungal agents such as posaconazole, isavuconazole, and echinocandins may be considered as alternative or adjunctive therapies [43]. For further therapy, recombinant cytokines, transfusions of granulocytes and prosthetic obturators, or the adjuvant use of hyperbaric oxygen are also utilized [44]. To prevent the infection from spreading further, the affected tissue must be surgically debrided right away. When necrotic tissue is present, aggressive surgical debridement is immediately carried out, resections of the face, partial pneumonectomy, colectomy, and other procedures are included, depending on the condition of the illness site, treatment with surgery is recommended for localized pulmonary lesions, cerebral disseminated, and rhino-orbital forms as well [42].

Regarding acute treatment, it has been established that all causative Mucorales species are resistant to some antifungal drugs, Therefore, treatment of mucormycosis relies on prompt and extensive surgical debridement of the infected tissue, effective control of hyperglycemia, and systemic antifungal therapy with liposomal amphotericin B given at 5 mg/kg/day three to four times per day. Note that despite the overwhelming evidence in support of liposomal amphotericin B, new drugs, such as isavuconazole, when given in licensed doses, and posaconazole, in the form of its delayed-release tablet, have also shown similar efficacy in large cohorts of patients with mucormycosis [45].

DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

8. Conclusion

Mucormycosis is a rare but serious fungal infection that impacts the sinuses, lungs, and sometimes the brain. This infection can also affect the skin when fungus enters through a cut, burn, or other type of injury to the skin, mucormycosis spreads quickly and requires urgent treatment, often involving aggressive surgery to remove infected tissue. It can also affect several parts of the body, but the most commonly reported are the rhino cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated types. The disease's clinical manifestations, outcomes, and risk factors allow for the classification of human mucormycosis into different hosts. Thus, early recognition and management lead to an improved prognosis for affected individuals.

References

[1] Lackner N, Posch W, & Lass-Flörl C. (2021). Microbiological and molecular diagnosis of mucormycosis: from old to new. Microorganisms. 9(7):1518.

[2] Ghosh D, Dey S, Chakraborty H, Mukherjee S, Halder A, Sarkar A, Chakraborty P, Ghosh R , Sarkar J. (2022). Mucormycosis: A new threat to Coronavirus disease 2019 with special emphasis on India. Clin Epidemiol Glob Health, 15: 101013.

[3] Bhatt K, Agolli A, Patel MH, Garimella R, Devi M, Garcia E, Amin H, Domingue C, Guerra Del Castillo R, SanchezGonzalez M. (2021). High Mortality Co-Infections of COVID-19 Patients: Mucormycosis and Other Fungal Infections. Discoveries. 9(1): e126

[4] Nair AS. (2022). Study assessing symptoms of anxiety, depression and sleep quality disturbances in post-Covid-19 Mucormycosis patients admitted for in-patient treatment admitted at a tertiary care hospital. Indian J Psychiatry. 64(Suppl3): S527.

[5] Madhavan Y, Sai KV, Shanmugam DK, Manimaran A, Guruviah K, Mohanta YK, Venugopal DC, Mohanta T, Sharma N, Muthupandian S. (2022). Current Treatment Options for COVID-19 Associated Mucormycosis: Present Status and Future Perspectives. J. Clin. Med. 11(13): 1-31.

[6] Muthu V, Agarwal R, Dhooria S, Sehgal IS, Prasad KT, Aggarwal AN, Chakrabarti A. (2021). Has the mortality from pulmonary mucormycosis changed over time? A systematic review and meta-analysis. Clinical Microbiology and Infection. 27(4):538-549.

[7] Singh AK, Singh R, Joshi SR, Misra A. (2021). Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 15(4), 102146.

[8] Mansoor S, Ahmed TI, Happa K, Sultan M, Manhas S, Shamas S. (2022). Spectrum of mucormycosis before and during COVID-19: epidemiology, diagnosis, and current therapeutic interventions. Curr Fungal Infect Repo. 16(4): 131-142.

[9] Al-Abbasi A. M, Abdil-Wahab A, Al-Jezani A R, Hashim H S, Al-Temimi D A, (2017). RHINO-ORBITO-CEREBRAL MUCORMYCOSIS IN BASRAH - IRAQ . Bas J Surg, December, 23

[10] Mohammad K, Ismael H , Shekhany K, Yashooa R, Younus D, Abdullah Kh , Alatraqchi, A, Aldabbagh R, Denning, D,. (2024). Fungal disease incidence and prevalence in Iraq − Preliminary estimates. Journal de Mycologie Médicale. 34. 100917.

[11] Downey MR, Taskar V, Linder DF, Baer SL, Waller JL, Bollag WB, Kheda M, Mohammed A, Padala S. (2022). Incidence and risk factors for mucormycosis in renal transplant patients. J Investig Med. 70(2): 396-401.

[12] Gupta I, Baranwal P, Singh G, Gupta, V. (2023). Mucormycosis, past and present: a comprehensive review. Future Microbiol. 18:217-234. doi: 10.2217/fmb-2022-0141.

[13] Hsu AJ, Tamma PD, Fisher BT. (2022). Challenges in the treatment of invasive aspergillosis in immunocompromised children. Antimicrob agents chemother. 66(7): e02156-21.

[14] Denning DW.(2024). Global incidence and mortality of severe fungal disease. The Lancet Infectious Diseases. 24(7). doi:https://doi.org/10.1016/S1473-3099(23)00692-8.

[15] Lelievre L, Garcia-Hermoso D, Abdoul H, Hivelin M, Chouaki T, Toubas D, Mamez, AC, Lantieri L, Lortholary O, Lanternier F. (2014). Posttraumatic mucormycosis: A nationwide study in France and review of the literature. Medicine (Baltimore), 93(24):395-404.

[16] Hussain MK, Ahmed S, Khan A, Siddiqui AJ, Khatoon S, Jahan S. (2023). Mucormycosis: A hidden mystery of fungal infection, possible diagnosis, treatment and development of new therapeutic agents. Eur J Med Chem. 246:115010.

[17] Sahu PS, Katwala J.(2022). Pathogenesis of Fungal Infections in the Central Nervous System: Host and Pathogen Factors in Neurotropism. Current Fungal Infection Reports. 16:221-223.

[18] Begum R, Thota S, Abdulkadir A, Kaur G, Bagam P, Batra S.(2022). NADPH oxidase family proteins: signaling dynamics to disease management. Cellular & Molecular Immunology. 19(6): 660-686.

[19] Loh JT. Lam KP.(2023). Fungal infections: immune defense, immunotherapies and vaccines. Advanced Drug Delivery Reviews. , 196:114775.

[20] Soleimanifar N, Assadiasl S, Rostamian A, Abdollahi A, Salehi M, Abdolmaleki M, Barzegari S, Sobati A, Sadr M, Mohebbi B, Mojtahedi H, Nicknam MH. (2023). Percentage of Th1 and Th17 cells and serum level of IL-17 and IFN-γ cytokines in COVID-19-associated mucormycosis. Med Mycol. , 61(8):myad090. doi: 10.1093/mmy/myad090. PMID: 37604786.

[21] Ibrahim AS, Kontoyiannis DP. (2013). Update on mucormycosis pathogenesis. Curr Opin Infect Dis. 26(6):508-515.

[22] Ibrahim AS, Spellberg B, Edwards J. (2008). Iron acquisition: A novel perspective on mucormycosis pathogenesis and treatment. Curr Opin Infect Dise. 21(6): 620-625.

[23] Alom S, Ali F, Zaman MK.(2021). A comperehesive Review on Mucormycosis (Black Fungus) and its Association with COVID-19. Current Trends in Pharmaceutical Research. 8(1):11-40.

[24] Borse SL, Wagh MS, Chaudhari SR, Naphade VD, Jadhav, A. G. (2022). A concise review on mucormycosis. Asian Pacific Journal of Health Sciences. 9(3):253-259.

[25] Chung ML, Widdel M, Kirchhoff J, Sellin J, Jelali M, Geiser F, Mücke M, Conrad, R. (2022). Risk factors for pressure injuries in adult patients: a narrative synthesis. Int J Environ Res Public Health. 19(2):761.

[26] Sahu S, Sharma S, Mandal S, Shrivastava P, Gupta K, Hait M. (2023). Impact of Mucormycosis on Health of Covid patients: a review. ES Food & Agroforestry. 13(2): 939.

[27] Gade V, Bajaj N, Sonarkar S, Radke S, Kokane N, Rahul N. (2021). Mucormycosis: Tsunami of Fungal Infection after Second Wave of COVID 19. Ann. Rom. Soc. Cell Biol. , 25(6): 7231-7238.

[28] Dam P, Cardoso MH, Mandal S, Franco OL, Sağıroğlu P, Polat OA, Kokoglu K, Mondal R, Mondal A, Mondal AK, Ocsoy I. (2023).Surge of mucormycosis during the COVID-19 pandemic. Travel med infect dis. , 52:102557.

[29] Jestin M, Azoulay E, Pène F, Bruneel F, Mayaux J, Murgier M, Darmon M, Valade, S. (2021). Poor outcome associated with mucormycosis in critically ill hematological patients: results of a multicenter study. Ann Intensive Care. 11(1):31.

[30] Darwish RM, AlMasri M, Al-Masri MM.(2022). Mucormycosis: the hidden and forgotten disease. Journal of applied microbiology. 132(6), 4042-4057.

[31] Dimaka K, Mallis A, Naxakis SS, Marangos M, Papadas, TA, Stathas T, Mastronikolis NS. (2014).Chronic rhinocerebral mucormycosis: a rare case report and review of the literature. Mycoses. , 57(11): 699-702.

DOI: 10.69946/ojms/2024.02.02.06, pp(47-55)

[32] Camara-Lemarroy CR, González-Moreno EI, Rodríguez-Gutiérrez R, Rendón-Ramírez EJ, Ayala-Cortés AS, Fraga-Hernández ML, García-Labastida L, Galarza-Delgado DA. (2014).Clinical features and outcome of mucormycosis. Interdiscip Perspect Infect Dis. , 2014: 562610.

[33] Lamoth F, Chung SJ, Damonti L, Alexander BD.(2017). Changing epidemiology of invasive mold infections in patients receiving azole prophylaxis. Clin Infect Dis. , 64(11): 1619-1621.

[34] Neto FMFD, Camargo PCLB, Costa AN, Teixeira RHOB, Carraro RM, Afonso JE, Campos SV, Samano MN, Fernandes LM, Abdalla LG, Pêgo-Fernandes PM. (2014).Fungal infection by mucorales order in lung transplantation: 4 case reports. Transplant Proc. , 46(6): 1849-1851.

[35] Li HM, Hwang SK, Zhou C, Du J, Zhang JZ.92013). Gangrenous cutaneous mucormycosis caused by Rhizopus oryzae: a case report and review of primary cutaneous mucormycosis in China over past 20 years. Mycopathologia. , 176(1-2):123-128.

[36] Riley TT, Muzny CA, Swiatlo E, Legendre DP.(2016). Breaking the mold: a review of mucormycosis and current pharmacological treatment options. Ann Pharmacother. , 50(9): 747-757.

[37] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ.(2005). Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. , 41(5): 634-653.

[38] Bernardo RM, Gurung A, Jain D, Malinis MF.(2016). Therapeutic challenges of hepatic mucormycosis in hematologic malignancy: a case report and review of the literature. Am J Case Rep. , 17:484-489.

[39] Rammaert B, Lanternier F, Zahar JR, Dannaoui E, Bougnoux ME, Lecuit M, Lortholary O. (2012).Healthcare-associated mucormycosis. Clin Infect Dis. , 54(1): 44-54.

[40] Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. (2012). Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis. ,54(suppl 1):S55-60.

[41] Pan American Health Organization/World Organization. (2021). Epidemiology Alert: COVID-19 associated Mucormycosis. , Washington, D.C: http://www.paho.org.

[42] Bharathi SA, Prakash A, Arul-Prakasam KC, Anbazhagan R. (2021). A Review: Mucormycosis. IJARESM. ,9(8): 1591-1598.

[43] Ghannoum MA, Perfect JR. Antifungal Therapy. CRC Press. USA. 2016.

[44] Sipsas NV, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP.(2018).Therapy of mucormycosis. Journal of Fungi. , 4(3): 90.

[45] Lax C, Nicolás FE, Navarro E, Garre V.(2024). Molecular mechanisms that govern infection and antifungal resistance in Mucorales. Microbiol Mol Biol Rev., 88(1), e00188-22.