International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 883-890 www.ijprajournal.com ISSN: 2456-4494

A Comprehensive Review on Mucormycosis

Dr Mrudangsinh Rathod[a], Mr Jaydev Patel*[a], Mr Manthan Prajapati[a], Mr Madhav oza[a]

a Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India.

Submitted: 25-09-2022 Accepted: 06-10-2022

ABSTRACT:
Aside from its history the incidence and pattern of mucormycosis have increased by the impression of Covid-19. Mucormycosis is the third most prevalent invasive fungal infection in children. Particularly patients with cancer are at high risk of this infection, however, there is not sufficient research on this population. It is highly prevalent in underdeveloped nations than rest of the world. Its underlying risk factors influence the clinical presentation, connections to immunosuppression, neutropenia, diabetes, and preterm birth have been found. To cure and diagnose mucormycosis is a challenge due to insufficient sensitivity and selectivity. The overall death rate is much higher despite extensive treatment, which includes disfiguring surgical debridement and sometimes additional toxic antifungal treatments. Amphotericin B (AmB) is still preferred, but other medicines such as Isavuconazole and Posaconazole are also recommended, depending on the clinical characteristics. In this review we have reviewed the epidemiology, pathophysiology, risk factors, clinical manifestations, diagnosis and treatment guidelines. In the near future, newer medicines like Rezafungin, SCY-078, Orolofim, and Encochelated Amphotericin B will expand therapy choices.

Keywords: Mucormycosis, Antifungal Agents, Fungal infections.

I. INTRODUCTION

Mucormycosis (previously zygomycosis), is an Angio invasive fungal infection caused by fungi of class zygomycetes and order Mucorales [1]. The most common types of fungi causing mucormycosis are Rhizopus and Mucor species. Other species include Rhizomucor, Syncephalastrum, Cunninghamella, Bertholletiae, Apophysomyces, Lichtheimia (formerly Absidia), and Saksenaea [2]. These fungi enter the body via the respiratory tract or skin and less commonly through the gastrointestinal tract eliciting an acute inflammatory response [3]. In immunocompromised patients it invades the blood vessels, causing serious vessel thrombosis and ischemic tissue necrosis [1]. Most commonly affects persons with comorbidities, like diabetes mellitus, chiefly diabetes ketoacidosis, long-term corticosteroid use, too much iron in the body, neutropenia, skin injury, prematurity, and low birth weight (for neonatal gastrointestinal mucormycosis) [1,4]. Mostly the mucormycosis infections were cutaneous (27%), gastrointestinal (21%), rhinocerebral (18%), and pulmonary (16%) & uncommon forms of infection are acute rhinocerebral and pulmonary mucormycosis [4,5]. In neonates, the most common mucormycosis infections were gastrointestinal (51%) and cutaneous (35.6%) [4]. These both have high mortality rates but gastrointestinal surpass cutaneous infection [4]. The mortality rates depend upon the patient's condition, type of fungus, and site of infection (For sinus infection mortality rates were 46%, pulmonary infection 76%, and for disseminated mucormycosis 96%) [3].

In the second wave of Covid 19, a large number of patients were infected from Covid which accelerates immune deficiency and the current prescribing of early steroids for a longer duration in avoiding the need for oxygen and hospital admission [6]. The activation of the immune system in Covid 19 infection leads to an increase in ferritin levels in the body [5]. Covid 19 is related to lymphopenia. So, diabetes, high ferritin, and lymphopenia collectively contribute to this steeper rise [4]. Another contributing factor is a new strain (Delta/Delta plus strain) of Covid 19 in the second wave in India is more infectious, causing more cases that might promote entry of Mucorales into the patients [5].

II. EPIDEMIOLOGY

Mucormycosis is becoming ordinary worldwide [7]. Due to a shortage of population-based studies, the prevalence rate of mucormycosis in India is unspecified. Mucormycosis is estimated

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 883-890 www.ijprajournal.com ISSN: 2456-4494

to have been 70 times quite frequent in India than in the rest of the world[8]as shown in Figure 1. The rate of mucormycosis in different countries per 100K[7].[7]. A. Chakrabarti., et. al 2001 in a 10 years case study from 1990-99 showed a prevalence rate of 12.9 cases/year from a total of 129 cases with 122 adult cases and 7 cases in children (aged < 10) [9]. In another successive study in 2006, A. Chakrabarti et. al, observed an increase in prevalence 35.6 cases/year from a total of 178 cases in a 5 years period with 5 cases in children (aged <10) and 173 cases (aged >11) [10]. In a study of 18 months A. Chakrabarti., et. al 2009, reported a prevalence rate of 50 cases/year of a total of 75 cases [11].

(Figure 1. The rate of mucormycosis in different countries per 100K[7].)

III. PATHOPHYSIOLOGY

The pathogenesis of mucormycosis starts off evolving with the inhalation or ingestion of sporangiospores or the inoculation of conidia in wounds or trauma [5]. Rare nosocomial outbreaks of mucormycosis had been related to infected bandages, clinical equipment, and airflow systems [5]. In wholesome individuals, mononuclear and polymorphonuclear phagocytes (PMNs) take away fungal spores and hyphae by oxidative and non-oxidative destruction mechanisms [12]. The blowup of the organism is facilitated via means of defects in phagocytic activity (e.g., neutropenia, hyperglycemia, acidosis or defects in phagocyte function) [5]. Mucormycosis can invade blood vessels, with subsequent thrombosis and tissue necrosis and can facilitate angioinvasion [13].

One trait that contributes to a cell's success is its ability to acquire iron. This resource is required by most organisms for growth and development [14]. A study conducted on patients with DKA revealed a critical role of the unbound iron level in their predisposing state [15,16]. In mammals, iron is bound to ferritin, transferrin, and lactoferrin, which can avoid the toxic effects of free iron [14,15]. Its ability to accept electrons makes it a useful tool for cellular oxidation-reduction. Microorganisms' capacity to transfer iron intracellularly is limited by insoluble Fe3+ hydroxides [17]. Rhizopus sp. uses deferoxamine to get the previously unavailable iron although it is an iron chelator [13].

IV. RISK FACTORS

Neutropenia, hematologic malignancy, diabetes mellitus, and haematopoietic stem cell transplant (HSCT) are common risk factors for mucormycosis [18].

Immunocompromised individuals, such as those with haematological malignancies, recipients of haematopoietic stem cells transplant (HSCT), solid organ transplants (SOT), diabetic patients with ketoacidosis, premature babies, people with trauma or burns on deferoxamine are the most affected. Paediatric studies, advocates age of <12 months being an independent risk factor for death [19,20,4]. While some researchers have shown an increase in adult prevalence, epidemiological data in children is insufficient to provide trends [21]. The growing prevalence of diabetes mellitus, and the increased usage of immunosuppressive therapies, contributes to the increased incidence of mucormycosis [22]. Surgical trauma and use of contaminated bandages, sticky dressings, wooden tongue depressors, and central venous catheters cause mucormycosis [23,24,25]. The real impact in the pediatric context is difficult to determine because of the disease's rarity and clinician's limited awareness of how to diagnose and document these cases [26].

V. CLINICAL FEATURES AND DIAGNOSIS

The maximum common sorts are rhinocerebral, pulmonary, cutaneous, and gastrointestinal infections [23]as shown in Figure 2. Clinical features based on the clinical type of mucormycosis[3].[3]. Dissemination happens in 32% to 38% of pediatric instances and more than 50% of neonatal instances [4,19,26]. The distribution of ailment is inspired appreciably through underlying chance factors [27]. Rhinoorbitocerebral sinus illness is the commonest manifestation in patients with diabetes and is often related to diabetic acidosis [27]. Children with pulmonary mucormycosis often have progressive pneumonia associated with pulmonary necrosis, hemoptysis, and spread to adjacent structures [27].

(Figure 2. Clinical features based on the clinical type of mucormycosis[3].)

The overall degree of diagnosis depends on the availability of imaging techniques, Histopathology, Molecular-based methods and Direct microscopy.

A higher index of suspicion, understanding of host variables, and early assessment of clinical symptoms are all required

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 883-890 www.ijprajournal.com ISSN: 2456-4494

for the diagnosis of mucormycosis. Diplopia in a diabetic patient or pleuritic symptoms in a neutropenic patient could be signs of infection, prompting the use of imaging modalities and the following collection of specimens for histology, microbiology, and advanced molecular testing. As previously stated, rhinocerebral, pulmonary, soft tissue and disseminated disease are the most common clinical presentations of Mucorales infection; yet, nearly any organ can be affected [28]. The diagnosis protocol remains the same for both pediatric and adult patients.

5.1 Imaging

The clinical method of diagnosis is ineffective in terms of sensitivity and specificity. Mucormycosis may cause necrotic cutaneous lesions in immunocompromised individuals, however additional infections such as Aspergillus, Fusarium, Pseudallescheria, and Scedosporium species should be considered [29].

A pulmonary computed tomography (CT) test is advised in patients with hematological malignancy and probable pulmonary mucormycosis to discover reversed halo sign, a spot of floor glass opacity encircled by a hoop of consolidation on thoracic CT, or vascular occlusion on CT pulmonary angiography. A cranial CT or magnetic resonance imaging (MRI) is particularly indicated in diabetics with facial pain, sinusitis, proptosis, ophthalmoplegia, or newly diagnosed amaurosis, or both, to verify if sinusitis is present [30].

Even before visualization symptoms, early CT findings in immunocompromised individuals at high risk for invasive pulmonary mucormycosis may identify pulmonary or sinal lesions in the absence of radiological abnormalities on conventional radiographs [31].

Clinical characteristics are difficult to differentiate from those of pulmonary aspergillosis or fusariosis. Furthermore, in tuberculosis-endemic areas, the two diseases may coexist [32].

In a recent study, 24 individuals with pulmonary mucormycosis had their CT scans compared to 96 patients with invasive lung aspergillosis the RHS was seen in 54% of individuals with mucormycosis but only 6% of those were associated with aspergillosis [33]. While all of these investigations lead to mucormycosis, a definitive diagnosis needs laboratory techniques such as histopathology and cultures [28].

5.2 Histopathology

In individuals with pulmonary mucormycosis, a definite diagnosis is predicated on the presence of fungal hyphae characteristic of mucormycetes in biopsies of afflicted tissues or bronchoalveolar lavage (BAL). Histopathology is a crucial diagnostic technique because it separates the presence of the fungus as a pathogen in the sample from a culture contaminant and is required to determine whether blood vessel invasion has occurred [34].

Mucorales organisms in tissue may be difficult to identify and interpret histologically. As a result, immunohistochemical stains, fluorescence and in situ hybridization, or in situ polymerase chain reaction (PCR) may be employed to describe and recognize genera within the order Mucorales. The in situ hybridization molecular diagnostic technique may eventually enhance the quick and early diagnosis of mucormycosis, although it, like other approaches such as immunohistochemistry, is still under research [31].

5.3 Direct Microbiology

Direct microscopy of KOH wet mounts can be visualized for a quick presumptive diagnosis of mucormycosis. It may be used on all samples delivered to the clinical laboratory, ideally with fluorescent brighteners as Blankophor and Calcofluor White in combination with KOH to facilitate visualization of the distinctive fungal hyphae, which in this instance necessitates the use of a fluorescent microscope [31].

A team of specialists from the European Confederation of Medical Mycology, in collaboration with the Mycoses Study Group Education and Research Consortium (ECMM/MSG ERC), strongly recommends it, along with histopathology [30].

5.4 Culture

Culture of specimens is necessary for the diagnosis of mucormycosis since it enables for genus and species identification, as well as antifungal susceptibility testing [31]. A positive culture from a sterile location confirms the diagnosis, and must be coupled with clinical and radiological evidence to establish a likely diagnosis [30]. However, culture's limited sensitivity is a major problem, since it might be erroneously negative in up to 50% of mucormycosis patients [31,35]. For an optimal yield, proper collection and treatment of the materials prior to inspection are required. As a result, when a case is suspected, strong communication and close coordination between physicians and microbiology laboratory are required to guarantee that all the diagnostic

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 883-890 www.ijprajournal.com ISSN: 2456-4494

procedure are completed correctly [29].

VI. TREATMENT

The treatment depends on the available surgical techniques and antifungal drugs [36]. Early diagnosis is necessary to alleviate tissue invasion and dissemination, but it remains difficult (even in high-risk patients) because of nonspecific symptoms that are commonly misrepresented to other infections [18]. ECMM and European Conference on Infections in Leukemia-6 (ECIL-6) strongly suggest surgery and control of underlying diseases: ketoacidosis and hyperglycemia treatment in diabetic patients, corticosteroid and immunosuppressive modulation and length of neutropenia, if feasible, lowering of blood pressure and growth factor [37]. Antifungal therapy is the cornerstone of mucormycosis treatment, and administration of any antifungal agent was strongly correlated with a 92 percent relatively lower risk of death in a study of pediatric mucormycosis cases [18].

6.1 Surgery

Localizations in the rhinoorbital or cutaneous regions are still simpler to operate on than those in the brain, lungs or other organ systems. When it comes to rhino orbito-cerebral forms, surgery has a direct impact on the therapy [38,39]. According to a 10-year clinicoepidemiological analysis, 65.2% of 184 patients underwent surgery compared to 21.4% of patients with haematological conditions [40]. Surgical debridement in conjunction with medical therapy was related with a better result than medical therapy alone. Surgery, on the other hand, is strongly advised whenever possible because of the supposed benefits [30]. Surgical debridement remains the same whether the patient is pediatric or not.

6.2 Drug Therapy

Both ECIL and ECMM suggest the use of Liposomal Amphotericin B (L-AmB) in adult patients [37]. Several studies over years suggests the usage of liposomal amphotericin B correctly handled mucormycosis with numerous organ involvement patterns [36]. The daily dose of L-AmB ranges from 1 mg/kg/day to 10mg/kg/day [36]. Patients receiving doses >5mg/kg and < 10mg/kg/day have increased response rates [36]. L-AmB dose <5mg are generally ineffective [37]. The current ECIL-6 guideline does not recommend Amphotericin B deoxycholate due to toxicity unless no other antifungal drug available [36]. Children tolerate Amphotericin B lipid complex (ABLC) at a dose of 5 mg/kg per day, although it is not advised in central nervous system (CNS) involvement [27]. Mucosal fungi are resistant to most antifungal drugs in vitro. Amphotericin B is the most effective drug, with the exception of Cunninghamella and Apophysomyces. Posaconazole and Isavuconazole, itraconazole and terbinafine are active against certain strains [28]. Posaconazole and Isavuconazole are moderately recommended by the guideline, but are strongly recommended if there is preexisting renal complication though therapeutic drug monitoring is recommended in Posaconazole only. Isavuconazole dosing is not recommended for children <13 years [41]. There are two days of loading doses of Isavuconazole (200 mg) every 8 hours, followed by one day of daily doses of 372 mg isavuconazonium sulphate (200 mg of Isavuconazole) per 8 hours [42]. No recommendations can be made for the paediatric population due to the fact that the experiment is still in progress. In addition, Isavuconazole is classified as a pregnancy class C medication. Due to the fact it is found in breast milk, nursing mothers should not be administered it [43]. Posaconazole of dose 40mg/ml oral suspension is used and is administered in dosage of 800 mg per day in two or four divided doses. The oral suspension of posaconazole has finite bioavailability but the newer tablet and intravenous formulations that achieve higher blood concentration and can widen the use of posaconazole as a first line treatment [44].

While facts do endorse a few degrees of assist for numerous combinations (amphotericin B plus triazoles/echinocandins), and mixture remedy can be rationalized because it seems to lack greater toxicity and has however, unproven benefit and are marginal recommended [41].

Iron chelators have been investigated as an additional treatment to reduce iron availability and hence limit fungal growth. The iron chelator Deferoxamine has been linked to an increase in mucormycosis incidence. Deferoxamine is a xenosiderophore, but the other two iron chelators, deferiprone and deferasirox, are not [45].
Experiments suggests Deferiprone prevented mucormycosis in diabetic mice [46]. In both diabetic and neutropenic animals Deferasirox shared the same effect and operated synergistically with AmB [47]. Also, three therapies were shown to be efficacious with L-AmB, micafungin and deferasirox [48].

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 883-890 www.ijprajournal.com ISSN: 2456-4494

6.3 Newer Drugs

New antifungal medication names include Rezafungin, SCY-078, Orolofim and Encochelated Amphotericin B are under clinical assessment [37]. Rezafungin a novel echinocandin against Mucorales has not been tested. SCY-078 is an underprivileged member of the novel glucan inhibitor subclass against Mucorales [49]. Olorofim is one of the orotomides, a major enzyme in pyrimidine biosynthesis, a newer anti-microbacterial class that inhibits dihydro-orotate dehydrogenase (DHODH). It's extremely active against Mucorales as well [50]. The new oral version of Amphotericin B is Encochleated Amphotericin B [51].

VII. CONCLUSION

Invasive mucormycosis necessitates a strong index of suspicion and immediate examination of clinical samples when the diagnosis is suspected. The illness usually progresses and is often deadly. Pediatric mucormycosis is very deadly illness that mostly affects children with malignancies and manifests lung, soft tissue, paranasal sinus, or widespread disease. When aggressive antifungal treatment and surgery are coupled, the outcome improves. To avoid contiguous spread and dissemination, surgical debridement should be considered and is typically required. Antifungal medication should be continued until clinical remission occurs, and recurrence should be monitored when treatment is stopped. A hospital-acquired illness should elicit a review of potential sources of contamination, with the goal of detecting any potential outbreaks early and implementing adequate source management. According to a recent study, strict adherence to the glycemic management strategy and low-dose steroids may lower [52]. The higher number of mucormycosis in India could be due to the prolonged use of steroids and weather conditions. Given the fact that mucormycosis is fetal in the pediatric population, further study on the management of mucormycosis is needed.

DECLARATIONS

i. Funding
Not applicable
ii. Conflicts of interest/Competing interests
No competing interest
iii. Ethics approval
Not applicable
iv. Consent to participate
Not applicable
v. Consent for publication
Not applicable
vi. Availability of data and material

Not applicable
vii. Code availability
Not applicable
viii. Authors' contributions
All authorshave equally contributed in the article.

REFERENCES

[1] Chakrabarti A, Singh R. Mucormycosis in India: unique features. Mycoses. 2014;57 Suppl 3:85-90.
[2] Bonifaz A, Tirado- Sánchez A, Calderón L, Romero- Cabello R, Kassack J, Ponce RM, Mena C, Stchigel A, Cano J, Guarro J. Mucormycosis in children: a study of 22 cases in a Mexican hospital. Mycoses. 2014 Dec;57:79-84.
[3] Mucormycosis [Internet] 2021 [cited February 25, 2021]. Available from https://www.cdc.gov/fungal/diseases/mucormycosis/index.html.
[4] Roilides E, Zaoutis TE, Walsh TJ. Invasive mucormycosis in neonates and children. Clinical Microbiology and Infection. 2009 Oct; 15:50-4.
[5] Reid G, Lynch III JP, Fishbein MC, Clark NM. Mucormycosis. InSeminars in respiratory and critical care medicine 2020 Feb (Vol. 41, No. 01, pp. 099-114). Thieme Medical Publishers.
[6] Upasana K, Rastogi N, Thakkar D, Yadav A, Arora S, Yadav S. Mucormycosis Surge with the Second Wave of COVID-19 in India. Authorea Preprints. 2021 May 24.
[7] Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. Journal of Fungi. 2019 Mar;5(1):26.
[8] Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Microorganisms. 2021 Mar;9(3):523.
[9] Chakrabarti A, Das A, Sharma A, Panda N, Das S, Gupta KL, Sakhuja V. Ten years' experience in mucormycosis at a tertiary care centre in India. Journal of Infection. 2001 Jul 1;42(4):261-6.
[10] Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, Rao P, Panda N, Verma SC, Sakhuja V. The rising trend of invasive mucormycosis in patients with uncontrolled diabetes mellitus. Sabouraudia. 2006 Jun;44(4):335-42.

[11] Chakrabarti A, Chatterjee SS, Das A, Panda N, Shivaprakash MR, Kaur A, Varma SC, Singhi S, Bhansali A, Sakhuja V. Invasive mucormycosis in India: experience in a tertiary care hospital. Postgraduate medical journal. 2009 Nov 1;85(1009):573-81.
[12] Kontoyiannis DP, Lewis RE. Invasive mucormycosis: update on pathogenesis, clinical manifestations, and management. Infectious Disease Clinics. 2006 Sep 1;20(3):581-607.
[13] Spellberg B, Edwards Jr J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clinical microbiology reviews. 2005 Jul;18(3):556-69.
[14] Howard DH. Acquisition, transport, and storage of iron by pathogenic fungi, Clin Microbiol Rev, 1999, vol. 12 (pg. 394-404).
[15] Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability, Diabetes, 1982, vol. 31 (pg. 1109-14)
[16] 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, vol. 91 (pg. 1979-86).
[17] Ibrahim AS, Spellberg B, Edwards J Jr. Iron acquisition: a novel perspective on mucormycosis pathogenesis and treatment. CurrOpin Infect Dis. 2008 Dec;21(6):620-5. doi: 10.1097/QCO.0b013e3283165fd1. PMID: 18978530; PMCID: PMC2773686.
[18] Otto WR, Pahud BA, Yin DE. Pediatric mucormycosis: a 10-year systematic review of reported cases and review of the literature. Journal of the Pediatric Infectious Diseases Society. 2019 Sep;8(4):342-50.
[19] Zaoutis TE, Roilides E, Chiou CC, Roden MM, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, et al. Zygomycosis in children: A systematic review and analysis of reported cases. Pedatr Infect Dis J. 2007; 26:723–7.
[20] 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):565–73.
[21] Prasad PA, Vaughan AM, Zaoutis TE. Trends in zygomycosis in children. Mycoses. 2012;55(4):352–6.
[22] Skiada A, Pagano LI, Groll A, Zimmerli S, Dupont B, Lagrou K, Lass-Florl C, Bouza E, Klimko N, Gaustad P, Richardson M. Mucormycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Mucormycosis between 2005 and 2007. Clinical Microbiology and Infection. 2011 Dec 1;17(12):1859-67.
[23] Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clinical Infectious Diseases. 2012 Feb 1;54(suppl_1):S23-34.
[24] Cheng VC, Chan JF, Ngan AH, et al. Outbreak of intestinal infection due to Rhizopus microsporus. J Clin Microbiol 2009; 47:2834–43.
[25] Skiada A, Petrikkos G. Cutaneous mucormycosis. Clin Microbiol Infect 2009; 15(Suppl 5):41–5.
[26] Pana ZD, Seidel D, Skiada A, Groll AH, Petrikkos G, Cornely OA, Roilides E. Invasive mucormycosis in children: an epidemiologic study in European and non-European countries based on two registries. BMC infectious diseases. 2016 Dec;16(1):1-9.
[27] Francis JR, Villanueva P, Bryant P, Blyth CC. Mucormycosis in children: review and recommendations for management. Journal of the Pediatric Infectious Diseases Society. 2018 May 15;7(2):159-64.
[28] A Skiada, C Lass-Floerl, N Klimko, A Ibrahim, E Roilides, G Petrikkos, Challenges in the diagnosis and treatment of mucormycosis, Medical Mycology, Volume 56, Issue suppl_1, April 2018, Pages S93–S101,
[29] Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. Journal of Fungi. 2020 Dec;6(4):265.
[30] Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, Hoenigl M, Jensen HE, Lagrou K, Lewis RE, Mellinghoff SC. 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. The Lancet infectious diseases. 2019 Dec 1;19(12):e405-21.
[31] Thomas J. Walsh, Maria N. Gamaletsou, Michael R. McGinnis, Randall T. Hayden, Dimitrios P. Kontoyiannis, Early Clinical and

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 883-890 www.ijprajournal.com ISSN: 2456-4494

Laboratory Diagnosis of Invasive Pulmonary, Extrapulmonary, and Disseminated Mucormycosis (Zygomycosis), Clinical Infectious Diseases, Volume 54, Issue suppl_1, February 2012, Pages S55–S60.

[32] Jiménez-Zarazúa O, Vélez-Ramírez LN, Alcocer-León M, Utrilla-Álvarez JD, Martínez-Rivera MA, Flores-Saldaña GA, Mondragón JD. A case of concomitant pulmonary tuberculosis and mucormycosis in an insulin-dependent diabetic patient Journal of clinical tuberculosis and other mycobacterial diseases. 2019 Aug 1;16:100105.

[33] Jung, J.; Kim, M.Y.; Lee, H.; Park, Y.; Lee, S.-O.; Choi, S.-H.; Kim, Y.; Woo, J.; Kim, S.-H. Comparison of computed tomographic findings in pulmonary mucormycosis and invasive pulmonary aspergillosis. Clin. Microbiol. Infect. 2015, 21, 684.e11–684.e18.

[34] Guarner, J.; Brandt, M.E. Histopathologic Diagnosis of Fungal Infections in the 21st Century. Clin. Microbiol. Rev. 2011, 24, 247–280.

[35] Lackner, M.; Caramalho, R.; Lass-Flörl, C. Laboratory diagnosis of mucormycosis: Current status and future perspectives. Future Microbiol. 2014, 9, 683–695.

[36] Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, Lass-Flörl C, Calandra T, Viscoli C, Herbrecht R. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. haematologica. 2017 Mar;102(3):433.

[37] Brunet K, Rammaert B. Mucormycosis treatment: Recommendations, latest advances, and perspectives. Journal de MycologieMédicale. 2020 Sep 1;30(3):101007.

[38] Gamaletsou MN, Sipsas NV, Roilides E, Walsh TJ. Rhino-orbital-cerebral mucormycosis. CurrInfect Dis Rep 2012;14:423–34.

[39] Vironneau P, Kania R, Morizot G, Elie C, Garcia-Hermoso D, Herman P, et al. Local control of rhino-orbito-cerebral mucormycosis dramatically impacts survival. Clin Microbiol Infect 2014;20:O336-339.

[40] Manesh A, Rupali P, Sullivan MO, Mohanraj P, Rupa V, George B, et al. Mucormycosis-A clinicoepidemiological review of cases over 10 years. Mycoses 2019;62:391–8.

[41] Steinbach WJ. Latest Thoughts on Treating Pediatric Mucormycosis. Journal of the Pediatric Infectious Diseases Society. 2020 Nov;9(5):640-4.

[42] Astellas Pharma US Prescribing information for Cresemba 2015. 2015. [Accessed January 15, 2016]. Available from: www.astellas.us/docs/cresemba.pdf.

[43] Donnelley MA, Zhu ES, Thompson GR 3rd. Isavuconazole in the treatment of invasive aspergillosis and mucormycosis infections. Infect Drug Resist. 2016 Jun 2;9:79-86. doi: 10.2147/IDR.S81416.

[44] Lewis RE, Kontoyiannis DP. Epidemiology and treatment of mucormycosis. Future microbiology. 2013 Sep;8(9):1163-75.

[45] Symeonidis AS. The role of iron and iron chelators in zygomycosis. Clin Microbiol Infect. 2009 Oct;15 Suppl 5:26-32.

[46] Ibrahim AS, Edwards Jr JE, Fu Y, Spellberg B. Deferiprone iron chelation as a novel therapy for experimental mucormycosis. Journal of Antimicrobial Chemotherapy. 2006 Nov 1;58(5):1070-3.

[47] Ibrahim AS, Gebermariam T, Fu Y, Lin L, Husseiny MI, French SW, Schwartz J, Skory CD, Edwards JE, Spellberg BJ. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. The Journal of clinical investigation. 2007 Sep 4;117(9):2649-57.

[48] Ibrahim AS, Gebremariam T, Luo G, Fu Y, French SW, Edwards Jr JE, Spellberg B. Combination therapy of murine mucormycosis or aspergillosis with iron chelation, polyenes, and echinocandins. Antimicrobial agents and chemotherapy. 2011 Apr;55(4):1768-70.

[49] Lamoth F, Alexander BD. Antifungal activities of SCY-078 (MK-3118) and standard antifungal agents against clinical non-Aspergillus mold isolates. Antimicrob Agents Chemother 2015;59:4308–11.

[50] Jørgensen KM, Astvad KMT, Hare RK, Arendrup MC. EUCAST Determination of Olorofim (F901318) Susceptibility of Mold Species, Method Validation, and MICs. Antimicrob Agents Chemother 2018;62.

[51] Van Daele R, Spriet I, Wauters J, Maertens J, Mercier T, Van Hecke S, et al. Antifungal drugs: What brings the future? Med Mycol 2019;57:S328–43.

[52] Mulakavalupil B, Vaity C, Joshi S, Misra A, Pandit RA. Absence of Case of Mucormycosis (March 2020–May 2021) under strict protocol driven management care

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 883-890 www.ijprajournal.com ISSN: 2456-4494

in a COVID-19 specific tertiary care intensive care unit. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021 Jun 9.

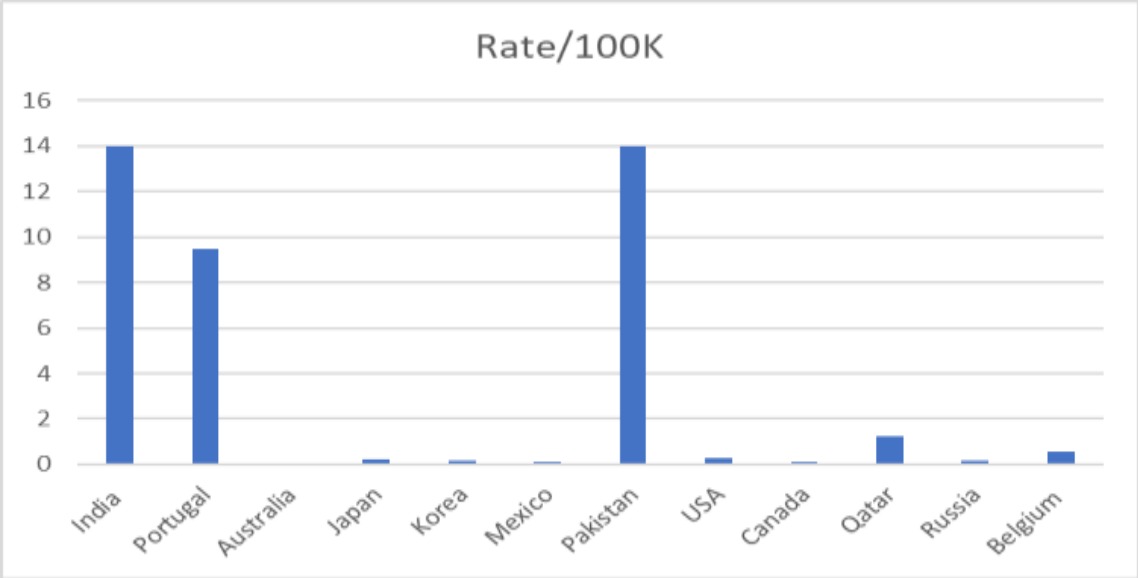

Figure 1. The rate of mucormycosis in different countries per 100K[7].

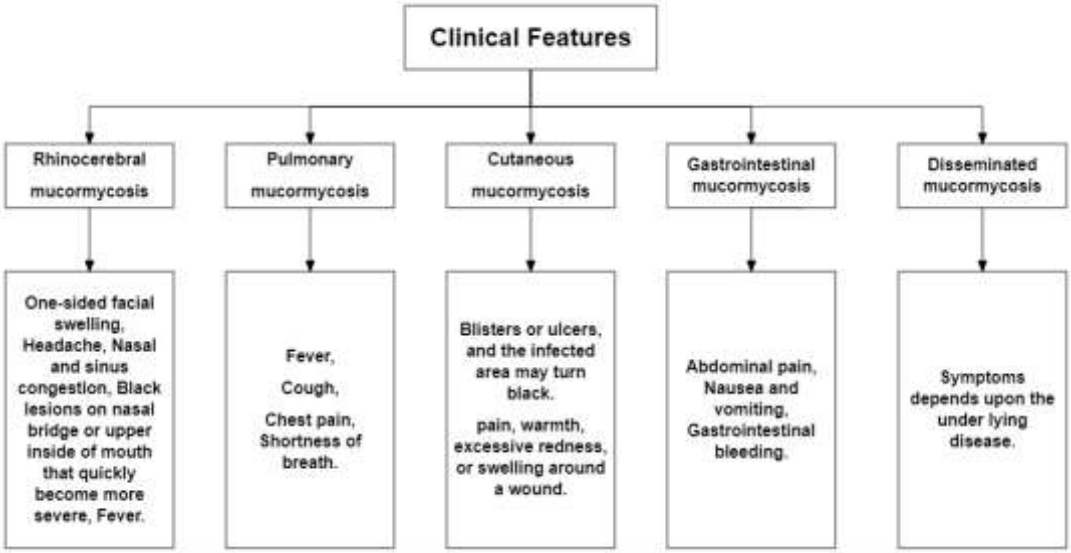

Figure 2. Clinical features based on the clinical type of mucormycosis[3].