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REVIEW ARTICLE ON ANTIFUNGAL AGENTS USED IN MUCORMYCOSIS

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ABSTRACT

Mucormycosis is a severe fungal infection caused by Mucorales fungi, which are found in soil and decaying organic matter. Immunocompromised people, such as those with severe COVID-19 disease, organ transplant recipients, cancer, or uncontrolled diabetes, are the main victims. The most prevalent kinds are disseminated, pulmonary, cutaneous, gastrointestinal, and rhino-orbital-cerebral. Fever, headaches, face discomfort, eyesight issues, and skin lesions are some of the symptoms. Microscopic analysis and tissue biopsy are frequently needed for diagnosis. Antifungal drugs and surgical debridement are the usual forms of therapy; nevertheless, because of the high death rates, particularly in instances that are widespread, early detection and intervention are essential.

KEYWORDS: Mucormycosis, fungal infection, immunocompromised, antifungal treatment, high mortality.

1. INTRODUCTION

A fungal infection known as mucormycosis is brought on by fungi that are members of the order Mucorales, which includes Lichtheimia species, Rhizopus species, Rhizomucor species, and Mucor species. Because these organisms are so similar in the environment, most people come into everyday contact with them.[1] Since mucormycosis is an opportunistic fungal infection, with the immune system compromised are more susceptible to contracting the disease. Recent data show a marked rise in mucormycosis because there more and more number of immune compromised patients suffering from hematopoietic stem cell disorders, diabetes, and hematologic malignancies. Financing: Under

the Max and Minnie solid organ transplant, or trauma, S.C.L. is the recipient of a Volcker Fund Young Investigator Award.[2] Particularly in people with impaired immune systems, invasive fungal illnesses are significant causes of morbidity and mortality.[3] Among these pathogens, Zygomycetes that cause mucormycosis (formerly known as Zygomycosis) are found around the globe and are becoming more common.[4] It accounts for 8.3–13% of all fungal infections found in haematology patients after autopsies.[5] A variety of chronic, sub-acute, and frequently rapidly developing illnesses cause by fungi belonging to the order Mucorales of the class Zygomycetes are referred to as "mucormycosis."[6] Mucormycosis can present with a variety of clinical manifestations, such as disseminated, pulmonary, cutaneous, gastrointestinal, sinusitis (including pansinusitis, rhino-orbital, or rhino-cerebral), and other unusual presentations.[7] The most frequent agents that cause mucormycosis are Lichtheimia spp., Rhizopus spp., Mucor spp., and Rhizomucor. Other genera that are less frequently linked to infection include Apophysomyces, Skeena, and Cunningham Ella.[8] These organisms are discovered within soil and decomposing organic substrates, making them widely distributed in the natural world.[9] Mucorales are spreading quickly and releasing a lot of spores into the atmosphere. Human comes in contact with those spores on a regular basis; an undamaged immune system keeps infections at bay. Therefore, immunocompromised people are the main victims of the illness. with severe underlying diseases, such as hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), uncontrolled diabetes mellitus, severe trauma, or burns, with the exception of victims of major natural disasters.[10] Despite being an uncommon disease, mucormycosis has terrible effects because it is linked to unacceptable high death rates, which can range from 20–50% in localized instances to 70–90% in cases of disseminated disease.[7] Mucorales have a predisposition for unionization in severely immunocompromised patients, which can lead to tissue infarction, necrosis, and spread. Conversely, cutaneous illness rarely spreads and is linked to better results.[11]

2. Types of Mucormycosis

Depending on the site of infection, mucormycosis may manifest in various forms:

2.1 Rhino cerebral Mucormycosis

Mucorales infections of the head and neck occur in distinct phases. Starting from the palate or paranasal sinuses, the virus moves to the orbit and, in the event of a delayed diagnosis, the brain. Any stage of this kind of infection will be referred to as "rhino-orbital-cerebral mucormycosis" for the sake of simplicity. Most commonly, rhino orbital cerebral mucormycosis is an infection.[12] Fever, sluggishness, headache, orbital pain, sudden blindness, 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 indication and manifestation that may be present. Additional concerns include internal carotid artery thrombosis and cavernous sinus. Cerebrospinal fluid results are typically vague or unremarkable.[7,13]

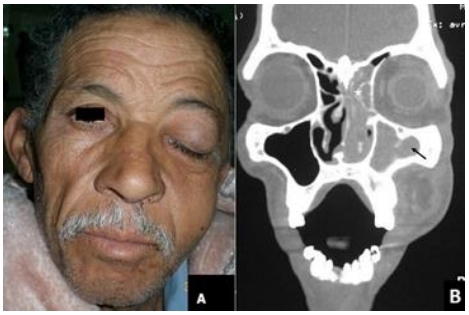

Fig. 1: Rhinocerebral mucormycosis.

2.2 Pulmonary mucormycosis

There was no particular lobar preference, however pulmonary consolidation, cavitation, or an effusion were observed less frequently. Following the administration of contrast, there have been reports of a “halo” sign (pen-infiltrate low attenuation) and rim enhancement on computed tomography.[14] Bronchoscopy was used to establish the majority of premortem diagnosis. The most often used method was transbronchial biopsy, while other successful methods include surgical excision, open lung biopsy, transthoracic needle aspiration, and broncho alveolar lavage.[15]

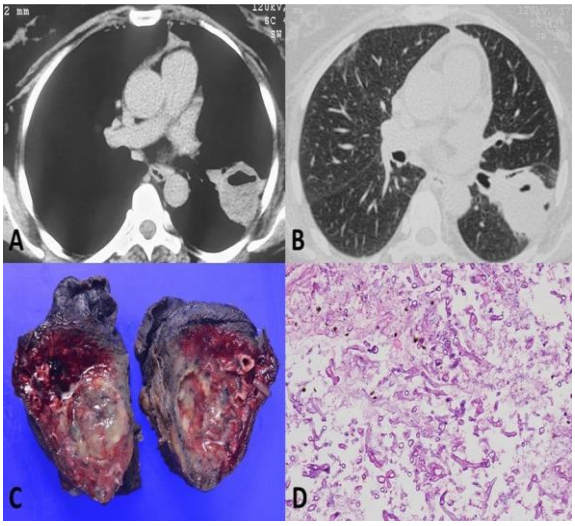

Fig. 2: Pulmonary mucormycosis.

2.3 Cutaneous mucormycosis

A break in the skin’s integrity caused by surgery, burns, soiled trauma, auto accidents, bone fractures, insect bites, cactus spine injuries, abrasions, lacerations, biopsy sites, allergen patch testing, contaminated adhesive tapes, and intramuscular injections can result in cutaneous mucormycosis.[16] Cutaneous mucormycosis may appear as a deep or superficial infection.[17] It may manifest as necrotizing cellulitis, echthyma gangrenosum-like lesions, blisters, nodules, pustules, or necrotic ulceration.[18,19,20] A skin biopsy is necessary to make a diagnosis. Wound swab in addition to fungi, culturesare not sensitive and can produce false microbiological results.[20]

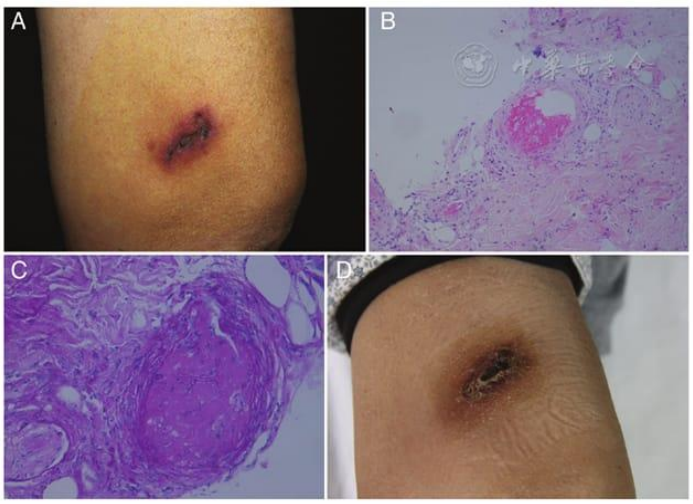

Fig. 3: Cutaneous mucormycosis.

2.4 Gastrointestinal mucormycosis

Abdominal discomfort, hematemesis, and melena are among the non-specific signs and signs of mucormycosis in the intestines.[21,22,23] Individuals suffering from acute myelogenous leukaemia, lymphoma, diabetic ketoacidosis, nonketotic diabetes mellitus, amoebic colitis, typhoid fever, pellagra, kwashiorkor, malaria, and those who have had organ, bone marrow, or peripheral blood stem cell transplants.[24]

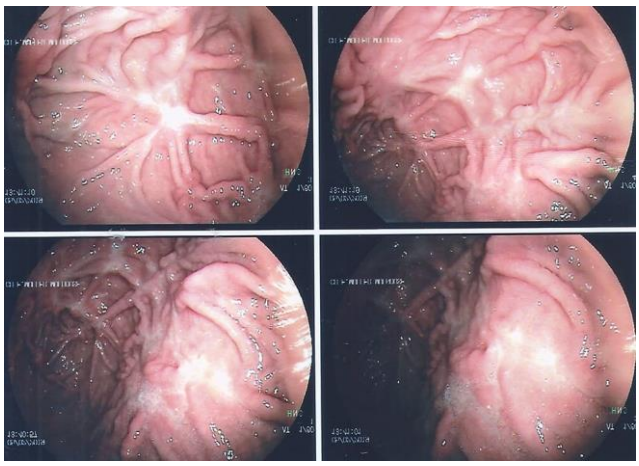

Fig. 4: Gastrointestinal mucormycosis.

2.5 Disseminated mucormycosis

Disseminated mucormycosis affects two or more organs that are not adjacent. The majority of disseminated mucormycosis patients are neutropenic people who have leukemia or lymphoma.[25,26] Dissemination occurs in 23-62% of instances of hematological malignancy.[26,27,28,29,30] Organ transplantation, chemotherapy, corticosteroids, and deferoxamine medication are additional risk factors for spreading.[28,32,34] Numerous individuals have infections from different viruses, bacteria, or fungi.[34,35] Disseminated illness has a death rate that is very close to 100%.[36,37]

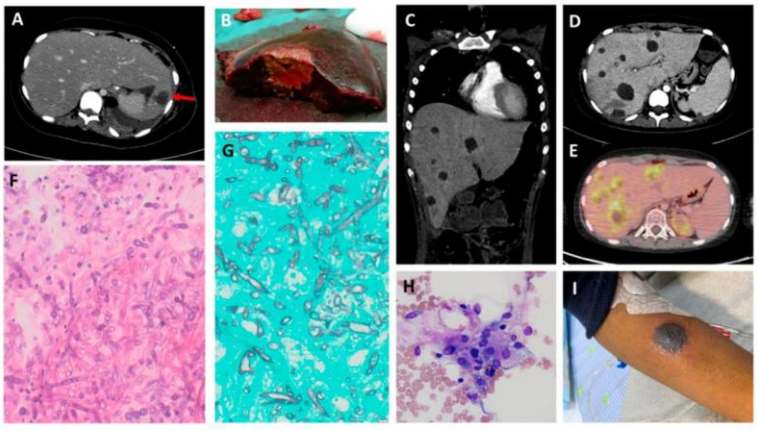

Fig. 5: Disseminated mucormycosis.

3. Mode of transmission

Patients with severe COVID-19, such as those in the intensive care unit (ICU), require extra care and hygienic practices due to their increased susceptibility to fungal and bacterial infections. In the last few months, reports of fungal infections aside from black fungus have been made worldwide. Apart from black fungus, aspergillosis or invasive candidiasis is the most typical fungal infection found in COVID-19 patients.[38] There are more reports of all these

fungal infections encompass various types and manifestations co-infections, which can all result in fatalities or very serious illnesses. Understanding the potential for co-infection by bacterial and fungal organisms is crucial for prompt diagnosis and treatment, which in turn helps to prevent significant disease and mortality from these infections, especially COVID-19.[39,40] Encompassing COVID-19. Some medical professionals speculate that this illness may have resulted from the use of steroid drugs during COVID-19 patient treatment, which were intended to minimize lung inflammation. Sadly, this both individuals with diabetes and those without diabetes patients blood sugar levels to rise during the SARS-CoV-2 pandemic.[41] Consequently, the patient's immunity has already been weakened For example, "Diabetes suppresses the immune system, the coronavirus aggravates it, and steroids used to treat COVID-19 act as gasoline on a fire." Decreases in immunity can also precipitate this dark fungal infection extremely quickly. Further details regarding the abrupt black fungal epidemic, symptoms, and other COVID-19 problems are provided in the upcoming section.[40]

4. Symptoms

The primary signs and symptoms of mucormycosis include fever, headache, and reddish-swollen skin around the eyes and nose during or after therapy for COVID-1942. Additionally, patients reported breathing shorter, eye swelling, ocular pain, face edema, and anomalies in their vision. Patients with diabetes have also reported experiencing diplopia, a symptom of infection.[43] According to scientific terminology, the main signs of a mucormycosis infection are proptosis, orbital apex syndrome, sinus pain, periorbital edema, ulcer of the palate, and cranial nerve palsy.[44] The most often reported instances of invasive mucormycosis. (19%) are the skin (19%), lungs (24%) and sinuses (39 percent). Most frequently, invasive mucormycosis.[45] In twenty-three percent of these situations, dissemination took place. Patients without underlying medical conditions have a mortality rate of 35%, diabetics have a mortality rate of 44%, and cancer patients have a mortality rate of 66%. The type of sickness and the infection site had an impact on the death rate. The researchers found that 96 percent of patients had widespread infections, 85 percent had gastrointestinal disorders, and 76 percent of patients with lung infections passed away. According to one study, children with mucormycosis manifested as pulmonary, gastrointestinal, rhinocranial, and cutaneous Infections were observed in 27%, 21%, 18%, and 16% of cases, respectively.[46]

5. Epidemiology

The underlying medical state of the patient determines the clinical appearance of mucormycosis. Overall, the most prevalent type is rhino-orbtio-cerebral mucormycosis (44–49%), which is followed by gastrointestinal (2–11%), pulmonary (10–11%), cutaneous (10–16%), and disseminated (6–11.6%).[47,48] Presentations in patients diagnosed with lung cancer and other hematological malignancies were followed by the most typical are diffuse and rhino-orbtio-cerebral presentations.[49] Mucormycosis is a minor subset of invasive fungal infections that affect recipients of solid organ transplants. Patients undergoing kidney transplants have a 0.2–1.2% incidence of mucormycosis; those undergoing liver transplants have 0–1.6%; those undergoing heart transplants have 0–0.6%; and those undergoing lung transplants have 0–1.5% incidence. Diabetes sufferers usually get pulmonary mucormycosis or rhino-orbtio-cerebral the underlying medical state of the patient determines the clinical appearance of mucormycosis. Overall, the most prevalent type is rhino-orbtio-cerebral mucormycosis (44–49%), which is followed by gastrointestinal (2–11%), pulmonary (10–11%), cutaneous (10–16%), and disseminated (6–11.6%). Presentations 3 in pulmonary cancer individuals suffering with hematological cancer were, then the most typical are diffuse and rhino-orbtio-cerebral presentations.[50] Mucormycosis is a minor subset of invasive fungal infections that affect recipients of solid organ

transplants. Patients undergoing renal transplants had an incidence of mucormycosis ranging from 0.2 to 1.2%, liver transplant patients from 0 to 1.6%, heart transplant patients from 0 to 0.6%, and lung transplant patients from 0 to 1.5%. Usually, pulmonary or rhino-orbitio-cerebral mucormycosis develops in diabetics. According to certain research, mucormycosis incidence is on the rise. For instance, the number of cases increased from eight per 100,000 admissions during 1989–1993 to 17 per 100,000 admissions during 1994–1998 at the M. D. Anderson Cancer Center in Texas, the overall postmortem incidence of mucormycosis was recorded at 0.7%, with 12 cases occurring out of a total of 1,765 autopsies conducted from 1989 to 1998.[51]

6. Risk Factors

A significant an increases risk of mucormycosis hematological malignancy, with leukaemia or lymphoma accounting for the majority of underlying diagnoses.[52] Aplastic anaemia, myelodysplastic syndrome, multiple myeloma, and sideroblastic anaemia are further haematological disorders linked to infection.[53,54] Mucormycosis in patients with solid tumours is uncommon.[52] Over a ten-year period, Kontoyiannis et al. It has been observed at M. D. Anderson Cancer Center that there were no cases of mucormycosis reported among patients diagnosed with solid tumours. All positive cultures indicated colonization.[51] Uncontrolled type 2 diabetes mellitus, particularly when combined with ketoacidosis, organ transplantation, neutropenia, malignant hematologic disorders, HIV, desferrioxamine therapy in patients undergoing haemodialysis, malnourishment, burns, and trauma are major risk factors for mucormycosis.[55] In developing nations, chronic renal disease and the aftermath of tuberculosis are significant issues.[56] Few studies have linked voriconazole use to the suppression of Aspergillus infections in transplant recipients.[57] Type 2 diabetes mellitus is very common in India and increases the chance of contracting the infection.[58] 40–100% of haematology patients with mucormycosis had been neutropenic at diagnosis, according to studies from different institutions.[58] While Kontoyiannis et al. discovered a Mean length Nosari et al. reported length of 10 days (range, 5-18 days) for neutronpenia prior to diagnosis, compared to a range of 16 days (5-74).[58,59] Individuals undergoing transplanting solid organ are also susceptible to mucormycosis, especially if they are receiving high-dose corticosteroids, OKT3, or anti-thymocyte globulin treatment for acute rejection.[60] Infection with CytomegaloviRus among recipients of solid organ transplants been linked to the emergence of mucormycosis.[61] Mucormycosis is more common among recipients of liver transplants as a result of bacterial infections, increase intraoperative blood transfusion needs, and retransplantation for graft failure.[61,62] Since neutrophils—as opposed to T lymphocytes—plays a significant role in defence against Mucorales, HIV infection does not seem to enhance the probability of developing mucormycosis.[63,64] When HIV patients do get mucormycosis, It is commonly observed that this condition arises as a consequence of intravenous drug use. In their analysis of HIV cases, Van den Saffele and Boelaert reported that 73% of patients diagnosed with mucormycosis had a history of intravenous drug use. Most of them experienced renal, cutaneous, articular, or brain infections.[65] Eighty to five hundred of those who use intravenous drugs and develop isolated cerebral mucormycosis (ICM) are HIV negative.[63,67] Mucorales infection may be predisposed in patients by further illness (such as malaria). Wilson et al. described a patient who had Aspergillus flavus and widespread AbsiDia corymbifera infection in addition to severe Plasmodium falciparum malaria. Severe haemolysis, metabolic acidosis, and immunological suppression from the malaria itself are potential predisposing factors.[66] mucormycosis has been associated with cirrhosis, congenital heart disease, malnutrition, and cancer, anaemia, hepatitis, glomerulo-nephritis, uraemia, amoebiasis, typhoid fever, and gastroenteritis.[67]

7. Diagnosis

Although diagnosing mucormycosis can be difficult, a skilled clinician can make the diagnosis based on identifying the disease's distinctive symptoms, a thorough clinical evaluation, a thorough patient history, and specialized testing. Since the galactomannan antigen test can be used to detect Aspergillosis, it is not effective in detecting mucormycosis.[68] In haematology patients, a diagnosis of mucormycosis is rarely suspected since most doctors assume invasive aspergillosis. Only 23–50% of instances involving haematology patients result in an ante mortem diagnosis of mucormycosis.[57,58,69] Chest computed tomography may reveal mucormycosis-related infiltrates that are not visible on a typical chest radiograph.[59,69] Diagnosis is difficult due to sputum culture's low sensitivity (25%).[57] There is no Increase in bronhoalveolar lavage yield.[57,70,71] The yield may be increased by transbronchial biopsy in addition to direct microscopy of bronchoalveolar lavage.[71,72] Given that many patients in the field of haematology are thrombocytopenic, obtaining a transbronchial biopsy may provide a challenge. A neutropenic or immunocompromised host's positive bronchoalveolar lavage result would be strongly suggestive of infection and should be handled as such.[70,71] The recommended method of diagnosis is Histological Examination of biopsied tissue. To confirm a diagnosis, histopathology must show invasion.[72] Polymerase chain reaction may become a diagnostic modality to identify these organisms.[73] Rickerts disseminated C was diagnosed by et al. bertholleTiae use a PCR technique that targets 18S ribosomal DNA in blood to detect infection in leukemic patient. Positive cultures from pleural fluid and bronchoalveolar lavage confirmed the diagnosis. Such an approach also holds promise for the finding that Aspergillosis is invasive.[73]

8. Antifungal Therapy

In the first decades of the previous century, antifungal treatments developed gradually. For instance, potassium iodide was the go-to medication for treating cutaneous fungal infections such as actinomycosis, blastomycosis, sporotrichosis, and tinea from the turn of the 20th century until the end of World War II.[74] Potassium iodide, which was initially isolated from sea algae, was thought to have a direct antifungal effect, however its exact mode of action is still unknown.[75] The rarity of mucormycosis has hindered the performance of prospective comparative trials comparing main treatments. As of right now, amphotericin B The US Food and Drug Administration (FDA) has licensed isavuconazole as one of the two antifungal medications for use as the primary treatment for mucormycosis. To reduce nephrotoxicity, an amphotericin derivative—ideally the liposomal form of amphotericin B—is the first line of treatment. Posaconazole, isavuconazole, and amphotericin B Deoxycholate are more alternatives. It may be thought to combine amphotericin B with either posaconazole or isavuconazole in patients whose condition is widespread or progressing quickly.[76] Final information are not accessible. While some papers have suggested combining various kinds of antifungal agents, more research is required to assess the effectiveness of this strategy. Benefits can include a reduced chance of resistance and faster fungicidal activity. The possibility of antagonistic reactions, additive or synergistic toxicity, increased drug-drug interactions, and increased expense are some possible drawbacks.[77]

8.1 Lipid Formulations of Amphotericin B

The effectiveness of amphotericin B in treating mucormycosis has been demonstrated. Based on efficacy and safety data, the medication of choice is the liposomal formulation. The recommended medication for the initial treatment of mucormycosis is amphotericin. Clinical research as well as in vitro and in vivo laboratory studies have demonstrated the effectiveness of amphotericin.[78] Clinical isolates of AMB have found to have high in vitro MICs the Cunningham Ella species, despite the lack of interpretationally defined breakpoints to AMB.[79] Nonetheless, a MIC for amphotericin

B of ≤0.5 μg/mL was substantially linked to better 6-week outcomes in a limited trial of non-Aspergillus invasive mold infections.[80] Amphotericin B lipid formulations (liposomal AMB, LAMB; and AMB lipid complex, ABLC) are thought to be the first-line treatment for mucormycosis because they have a higher therapeutic index than the traditional amphotericin B Deoxycholate.[81,82] The optimal dosage of AMB and its formulations for the treatment of mucormycosis remains undetermined, as is the case with numerous antifungal medications and mycoses. According to prevailing guidelines, the suggested daily dosage for ABLC and LAMB is 5 mg/kg/day.[83,84] Mucormycosis can also be treated with amphotericin B Deoxycholate, especially if other formulations prove to be too expensive. A dosage of 1-1.5 mg/kg/d is usual. Typically, 2.5–3 g is the total dose administered during therapy. This medication must be used in high doses, and nephrotoxicity may occur. This is especially concerning because a large number of people (such as diabetics and transplant recipients) who develop mucormycosis already have renal impairment. It is crucial to keep an eye on the renal function of patients using amphotericin B. If a patient's serum creatinine doubles from baseline, it may be time to switch to liposomal amphotericin B. Furthermore, while delivering any formulation of serum electrolytes (such as potassium, phosphorus, and magnesium), careful monitoring and replenishment of these electrolytes should be carried out. AMB's in vitro anti-Mucorales action varies greatly.[85]

8.2. New Triazole

Ergosterol is removed from the fungal cell membrane by Triazoles. Fluconazole, itraconazole, and voriconazole are triazole antifungals that exhibit negligible or no efficacy against Mucorales. More recent Triazoles, for instance, posaconazole and isavuconazole, have demonstrated improved in vitro efficacy against Mucorales, with clinical evidence recommending their application in mucormycosis.[86,87]

8.2.1. Posaconazole

The in vitro activity of posaconazole against Mucorales varies according on the species.[79] The median MICs of posaconazole for different Mucorales species ranged greatly between 1.0 and 8.0 μg/mL, according to a study of 131 clinical isolates.[88] Experimental infections caused by Mucor spp. Were most sensitive to posaconazole in animal investigations, but Rhizopus spp. Infections were typically non-responsive.[89,90] A serum concentration of posaconazole greater than 4000 μg/mL is required to inhibit the development of Rhizopus spp. With a minimum inhibitory concentration (MIC) of 2 μg/mL, as demonstrated by Lewis et al. in an lung mucormycosis model in immunosuppressed mice.[89] There are few clinical research on posaconazole effectiveness in treating mucormycosis. Posaconazole may be a salvage therapy option for individuals who are intolerant or resistant to LAMB, according to early case reports and case series.[91,92] The success rate of salvage therapy using posaconazole oral suspension (800 mg in 4 split doses) was 70% in a later open-label trial with 24 patients. The medication had just mild gastrointestinal adverse effects and was well tolerated.[93] Posaconazole oral suspension was utilized as salvage therapy in a cohort of 91 patients diagnosed with refractory mucormycosis, as reported in a separate retrospective analysis. The overall response rate was found to be 61%, while it increased to 65% among the subgroup of patients suffering from pulmonary mucormycosis. At the conclusion of the 12-week course of treatment, 21% more individuals had stable illness.[94] Posaconazole was the sole medication available up until recently. It used to be taken orally as an oral suspension, three or four times a day, with food (ideally a high-fat meal) or an acidic fizzy beverage to increase absorption. The use of the oral solution in critically sick patients is complicated by these dietary requirements since the patients may not be able to eat or may feel queasy.[95,96] Consequently, posaconazole oral suspension absorption was

frequently subpar, which resulted in treatment failures.[95] A gastro-resistant tablet and an intravenous (IV) solution have been developed to get around the pharmacokinetic constraints of the oral solution.[97]

8.2.2. Isavuconazole

The prodrug Isavuconazonium sulphate's physiologically active ingredient is a novel, broad-spectrum triazole called isavuconazole. In situations where amphotericin B is not viable, it has received approval for the treatment of mucormycosis in the United States and Europe. The recommended regimen includes an initial loading dose of 200 mg administered three times daily for a duration of two days, followed by a maintenance dosage of 200 mg per day thereafter. This medication is available in both intravenous and oral formulations. In contrast to azoles, isavuconazole has a number of advantages in terms of pharmacokinetics and safety.[99] These advantages include the absence of nephrotoxic cyclohexatriene in the IV formulation, excellent oral bioavailability without the need for food, less drug–drug interactions, less toxicity, particularly hepatotoxicity, skin and ocular side effects, and QT prolongation, as well as no need for dose adjustments in cases of kidney, liver failure, or obesity. Similar to posaconazole, isavuconazole has species-dependent variability in its in vitro efficacy against Mucorales.[100,101] It is important to remember that the minimum inhibitory concentration (MIC) of isavuconazole for Mucorales is two to four times higher than that of posaconazole. This should be considered in clinical practice.[100] Isavuconazole showed similar L-AmB at high doses is effective in reducing the tissue fungal burden in the neutropenic mouse model, of lung and brain of Rhizopus-caused mucormycosis, and it also improved survival after 21 days of treatment.[102] Isavuconazole has demonstrated efficacy as salvage therapy for mucormycosis in a number of case reports involving severely immunosuppressed patients, including instances of posaconazole failure.[103]

9. CONCLUSION

Mucormycosis fungal infection that brought by a collective of fungi called Mucormycetes, which are commonly found in soil, decaying organic matter, and the environment. It primarily affects immunocompromised individuals, for instance, those that possess with uncontrolled diabetes, organ transplants, cancer, or severe COVID-19 illness. The most similar types of mucormycosis are rhino cerebral (sinus and brain), pulmonary, cutaneous, gastrointestinal, and disseminated. Symptoms can include fever, headache, facial pain and swelling, vision problems, and skin lesions. Diagnosis often requires tissue biopsy and microscopic examination. Treatment typically involves a combination of antifungal medications, such as amphotericin B formulations, posaconazole, and isavuconazole, as well as aggressive surgical debridement. Timely diagnosis and intervention are critical, as mucormycosis can rapidly progress and has high mortality rates, especially in disseminated cases. Preventive measures, such as strict glucose control in diabetics, are also important to reduce the risk of this opportunistic infection.

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