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Mucormycosis: Covid's Deadly Companion

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ABSTRACT

The pandemic Covid-19 is continuing to spread around the world, with more than 200 million confirmed cases and four million deaths across nearly 200 countries. The SARS-CoV-2 was first identified in Wuhan, Hubei Province, China, in December 2019. The virus is primarily transmitted by inhalation or contact with infected droplets. The Second wave of COVID-19 is affecting most of the world but the scenario is very grim in India. The healthcare system collapsed in India during the second wave due to a surge in COVID cases leading to rise in opportunistic infections. Unfortunately, some Covid-19-treated patients develop Mucormycosis, also known as Black Fungus, which is a deadly infection. The mucormycosis epidemic in India has brought into sharp focus the seriousness of fungal infections and the relatively poor state of the science on their prevention, diagnosis, and management. Some of the variables responsible for the rise in mucormycosis cases in India include the inappropriate use of steroids and other immunomodulators, contaminated oxygen supplies, and poor glycemic management in a population with a pre-existing risk of diabetes. Diabetes was discovered to be the most significant risk factor of them all. The current review mainly focuses on all the possible aspects for the rise in mucormycosis in covid patients in India along with its severity, diagnosis and treatment.

INTRODUCTION:

Coronaviruses are a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans being highly transmissible, this novel coronavirus disease 2019 (COVID-19), has spread fast all over the world [1].WHO declared coronavirus disease 2019 (COVID-19), as a global pandemic in March 2020. Till now more than 200 million cases of covid-19 are being reported worldwide. India is rated second in the number of covid cases. In terms of infectiousness, severity, and symptoms, the lethal second wave of the COVID-19 pandemic that attacked India in April-May was substantially different from the first wave that struck in 2020. The upsurge in the cases in India during the second wave was mainly driven by the delta variant which was first detected in the South Asian nation and has now spread to over 80 countries. At the height of its second wave in May, India was seeing more than 400,000 confirmed daily infections far higher than the 97,000 per day peak it experienced last September. This escalation in the covid cases had made a way for the rise in opportunistic infections. Secondary infections are widespread in hospitalized, critically ill Covid-19 patients, accounting for 10 to 30 percent of cases, with fungal infections being 10 times more likely. One such opportunistic infection is Mucormycosis which although has a low incidence rate, varying from 0.005 to 1.7 per million populations globally [2]. In the aftermath of the continuing coronavirus pandemic, many instances have been seen recently, indicating a major increase in its incidence. It's the third most prevalent invasive fungal infection, and it's associated with a high rate of morbidity and mortality [3]. Mucormycosis has a 46 percent fatality rate worldwide [4]. It was reported that a large majority of the mucormycosis patients, constituting 84.4 percent, had a history of coronavirus disease.

Mucormycosis or Zygomycosis is a rare, angioinvasive, rapidly progressive, and life-threatening fungal infection caused by ubiquitous fungus that belong to class Zygomycetes and order Mucorales [5]. Mucormycosis is defined by tissue infarction and necrosis in the host tissues as a result of hyphae invading the vasculature [6]. The most frequently reported pathogens in mucormycosis *are Rhizopus spp, Mucor spp,* and *Lichtheimia spp,* followed by *Rhizomucor spp, Cunninghamella spp, Apophysomyces spp, and Saksenaea spp* [7]. *Rhizopus arrhizus* been the most common agent causing mucormycosis in India and globally [8] followed by *Apophysomyces variabilis*. *Rhizopus arrhizusis* is responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino-orbital-cerebral (ROCM) form [2,9].

While several treatment options for COVID-19 have been evaluated, none except systemic glucocorticoids have been shown to improve survival in COVID-19. Use of systemic glucocorticoids to improve survival in COVID-19 has triggered mucormycosis to a greater extent. Major factors such as Diabetes mellitus, COVID-19, the widespread use of steroids, broad-spectrum antibiotics, antiparasitics, antivirals as a part of cocktail therapy used against COVID-19 even in mild cases with no strict prescription checks in India and most drugs including glucocorticoids readily available over the counter had led to surge in Mucormycosis cases in India [10].

Mucormycosis is difficult to diagnose. As a result, early diagnosis and treatment are critical, as even a 6-day delay doubles 30-day mortality from 35 percent to 66 percent [5]. Despite early diagnosis and aggressive combined surgical and medical therapy, the prognosis for recovery from mucormycosis is poor [11]. Four general principles are critical for managing mucormycosis: rapid diagnosis, reversal of underlying predisposing factors, surgical debridement of infected tissue and appropriate antifungal therapy [12]. Liposomal Amphotericin B has been the drug of choice for its treatment.

PREVALENCE:

More than 45,432 cases of mucormycosis and over 4,000 deaths by mucormycosis have been reported by states and Union territories (UTs) across India. The previous study reported 101 cases of Covid-19 patients contracting mucormycosis, a rare but serious fungal infection [2]. Diabetes mellitus was discovered to be the single most important risk factor, afflicting 83 of the 101 participants. In India, the computational-model-based strategy predicted a prevalence of 14 incidents per 100,000 people [11,8]. Overall mortality was noted in 36.5% in India compared to 61.9% globally [13]. Especially the intracranial involvement of mucormycosis increases the fatality rate to as high as 90% [14].

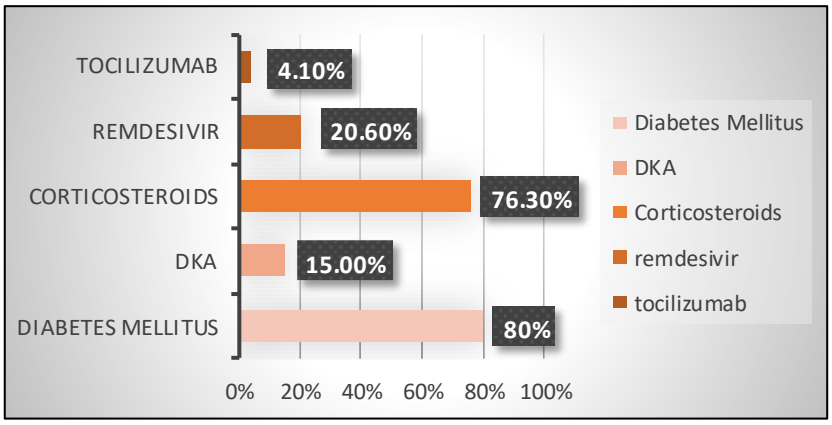

Figure No.1: Prevalence of Mucormycosis [2]

As shown in Figure No. 1, Pre-existing Diabetes mellitus (DM) accounted for 80% of cases, while concomitant Diabetic ketoacidosis (DKA) was present in nearly 15% of people with mucormycosis and COVID-19. History of corticosteroid intake for the treatment of COVID-19 was present in 76.3% of cases, followed by remdesivir (20.6%) and tocilizumab (4.1%). The commonest organ involved with mucormycosis was the nose and sinus (88.9%), followed by rhino-orbital (56.7%).

CLINICAL MANIFESTATION OF MUCORMYCOSIS:

The clinical presentations of mucormycosis are classified based on anatomic localization, such as rhino-orbital-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal, and disseminated mucormycosis [15]. When it comes to COVID-19, there are two types of mucormycosis commonly observed in patients such as Rhino-Orbito-Cerebral Mucormycosis (ROCM) and Pulmonary Mucormycosis.

Saprophytic fungi cause rhinocerebral mucormycosis, a rare opportunistic infection that starts in the nasal passages and progresses via the sinuses to infect the orbit and, eventually, the brain [16]. Tissue necrosis caused by angioinvasion and subsequent thrombosis is the disease's hallmark in rhinocerebral mucormycosis. This presents as notoriously black, necrotic eschar. People with uncontrolled diabetes and those who have had a kidney transplant are more likely to get rhinocerebral mucormycosis [17].

In immunocompromised patients, inhalation of sporangiospores appears to be the major route of infection, resulting in pulmonary infection. It affects the lungs and respiratory system, unlike ROCM. Patients with significant neutropenia, graft versus host illness, and

hematological malignancies are more likely to develop pulmonary mucormycosis, whereas diabetic patients are more likely to develop rhino-orbital disease [18].

SYMPTOMS:

If the intracranial extension is present, rhinocerebral mucormycosis can present with atypical signs and symptoms similar to complicated sinusitis, such as nasal blockage, crusting, proptosis, facial pain and edema, chemosis, and even ophthalmoplegia, as well as headache, fever, and various neurological signs and symptoms. A black eschar in the nasal cavity or over the hard palate region is seen very often but is not characteristic [19]. Patients may experience impaired vision, orbital inflammation, sinusitis, eye and facial pain or numbness, or even periorbital cellulitis over time. Fever, cough, shortness of breath, and chest pain are all common signs of pulmonary mucormycosis [20].

PATHOPHYSIOLOGY:

Firstly, COVID-19 has been linked to severe pulmonary parenchymal illness. Post mortem study of COVID-19 patients revealed the diffuse alveolar injury, substantial hyaline membrane formation, interstitial lymphocyte infiltration, and vascular microthrombi production. These pulmonary changes may take weeks to resolve and thus may serve as a nidus for fungal infection [21].

Secondly, COVID-19 is associated with severe immune system abnormalities–reduced CD4+ and CD8+ T-lymphocyte counts; elevated inflammatory cytokines such as interleukin (IL)-2R, IL-6, IL-10 and tumor necrosis factor-alpha [22]. Free available iron is an ideal resource for mucormycosisinCOVID-19 patients due to increased levels of cytokines especially IL-6, which leads to an increase in synthesis and decrease in iron transport, resulting in an increase in free iron level [2].

Thirdly, severe COVID-19 causes mechanical ventilation and a protracted stay in the intensive care unit, which can lead to bacterial co-infections and IFIs [23].

Finally, glucocorticoids have been used extensively to reduce hospital stay and mortality related to COVID-19. Dexamethasone and methylprednisolone have both been widely used in COVID-19 infection especially in moderate to severe cases. Due to the immunosuppressive nature of glucocorticoids, patients become more susceptible to secondary infections [24].

Previous studies suggested that SARS-CoV-2 itself might induce an immunosuppressive state that exposes the patient to the risk of developing opportunistic infections. These kinds of infections by themselves are associated with the worst outcome, especially when the immune system response does not improve. However, on the improvement of the immune these opportunistic infections might be controlled [25].

RISK FACTORS INVOLVED IN COVID PATIENTS:

Diabetes, steroids, antibiotics, and nosocomial infections are the greatest risk factors for mucormycosis in COVID-19 patients, while zinc supplements, monoclonal antibodies, cancer and transplant, and iron chelators are minor risk factors as shown in figure no. 2.

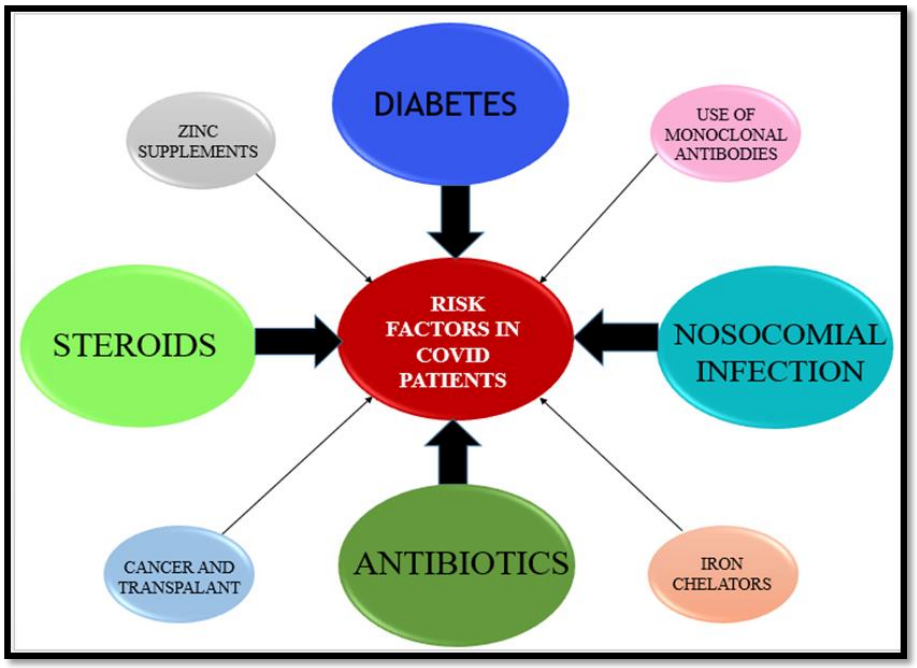

Figure No. 2: Risk factors involved in COVID patients

1. Diabetes:

India has the second-largest number of adults aged 20–79 years with Diabetes Mellitus (DM). DM is the single most common risk factor for mucormycosis in India, accounting for more than half of all cases [26]. Diabetes mellitus is responsible for the ROCM (Rhino orbital cerebral mucormycosis) type of disease [3]. A recent multicenter study from India reported that 77% of ROCM cases were in the diabetic population [27].

Host Defense: Iron is required for cell growth and development, and it plays a role in a variety of cell functions [28]. Mucorales can acquire iron from the host. In mammalian hosts,

iron is bound to host carrier proteins, such as transferrin, ferritin, and lactoferrin. This sequestration avoids toxic effect of free iron. This technique of restricting iron availability is also a major universal microbe defense mechanism [29].

Fungal Attack: Rhizopus is unable to sequester iron from iron-binding proteins. The chronically elevated blood glucose levels in diabetic patients will lead to an impaired neutrophil function. Hyperglycemia and an acidic pH in Diabetic ketoacidosis can cause a defect in neutrophil motility and killing of bacteria and fungi. It is believed that the acidic pH leads to the dissociation of iron-protein complexes, which allows the fungal cells to utilize free iron and promote their growth [29].The importance of good glycemic control during the COVID-19 pandemic is emphasized. Regular monitoring of blood glucose is important.

2. Steroids:

Steroids help in fighting COVID-19 act as double-edged sword paving a way for invasive fungal infections. ICU patients infected with SARS-CoV-2 are given corticosteroids because the quantity of white blood cells and neutrophils, as well as levels of procalcitonin, C-reactive protein, and other inflammatory indices, are much higher in ICU cases than in non-ICU cases [30]. ICMR in their clinical guidance for management of Covid-19 had mentioned the use of steroids in moderate to severe disease. The on ground cause of rise in mucormycois in covid patients has been the excessive and injudicious use of steroids. The physician has been prescribed it too early during the disease. Overdose and prolonged use of steroids make the lungs fertile ground for fungal infections.

The RECOVERY trial is the world's largest clinical trial into treatments for COVID-19, with more than 30,000 participants across 177 trial sites in the UK [31]. According to this trial, dexamethasone, a low-cost steroid treatment, reduces the fatality rate of hospitalized COVID-19 patients with severe respiratory problems by up to one third. The same trial also showed that if it was given for patients who did not require respiratory support, who did not require oxygen, who were not severely ill, it had a detrimental effect. So, the trial was very clear in stating that there is an appropriate time and place for using the steroids, in a select group of patients who require oxygen or ventilators not in mild cases [19].

In moderate cases, methylprednisolone should be given intravenously at a dose of 0.5-1 mg/kg/day for three days as per Indian guidelines. In severe cases, the dose should be increased to 1-2 mg/kg/day for three days [32]. National Institute of Health also recommends

the use of dexamethasone (6 mg per day for a maximum of 10) in ventilated patients or those who require supplemental oxygen, excluding milder cases [5]. However, some patients were given 30 mg of dexamethasone per day, which is five times the permissible limit. Others were given dexamethasone for 20 to 30 days in a row. Mucormycosis was caused by even a short course of steroid medication (5–14 days) or too early prescribing, especially in persons with DM [33].

Immunocompromised patients are predisposed to mucormycosis if they have received a cumulative prednisone dose of more than 600 mg or a total methyl prednisone dose of 2-7 g in the preceding month [34]. Surprisingly, in the European Confederation of Medical Mycology study, 46 percent of the patients had received corticosteroids within the month before the diagnosis of mucormycosis [35]. Therefore, early use of steroids in covid-19 treatment may lower the body's immunity and can also cause viral replication, thus worsening the situation.

3. Nosocomial infection:

Industrial oxygen is produced like medical-grade oxygen. However, the containers carrying medical oxygen need to comply with certain prescribed norms so that they do not alter the safety, identity, strength, quality, or purity of the oxygen [13]. A study from North India reported that 9% of the mucormycosis cases are nosocomial in origin [36]. According to this study, contaminated intramuscular injections and surgery, adhesive tapes, and endobronchial tubes, were sources of infection in nosocomial mucormycosis. Major culprit in CAM (Covid Associated Mucormycosis) cases was the shortage and contamination of oxygen cylinders in India which led people to pull oxygen cylinders from wherever possible, some of which were even outdated and were also colonized by the fungus. Ideally, immunocompromised patients should be kept in isolation rooms with positive pressure but to protect healthcare workers from COVID-19, it was recommended to keep COVID-19 positive patients in negative pressure rooms. It was demonstrated that patients admitted in negative pressure ICU rooms were at higher risk of secondary infections [37]. Use of contaminated water in humidifiers, non-medical grade industrial oxygen cylinders, nonsterile humidifier bottles led to an increase in mucormycosis cases through the spread of fungal spores [38].

4. Use of monoclonal antibodies:

Tocilizumab is an immunosuppressive humanized monoclonal antibody drug. With COVID-19, people can be at risk of cytokine storms as their bodies continue to ramp up their immune

system to fight off the infection. Tocilizumab works by suppressing IL-6, which helps to quiet down the immune system and regulate cytokine storms. It is not an antiviral medicine and may only be beneficial in a subset of individuals who have corona virus-induced inflammation and lung damage. The crucial factor to remember is that too much Tocilizumab production and activity might lead to autoimmune disorders and tissue damage [39]. In this way, it could further increase the risk of secondary infections in COVID-19 patients [40].

5. Use of zinc supplements:

Current research suggests that zinc may lessen the risk, duration and severity of SARS-CoV-2 infections, particularly in individuals at risk of zinc deficiency including people with chronic disease co-morbidities and older adults [41]. However, zinc (Zn) starvation inhibits microbial growth in tissues and is a crucial element in pathogenesis of fungal infection. By limiting the function of Zn-binding proteins, which are mostly transcription factors involved in many biological processes, Zn deficiency causes stress in fungal cells and inhibits fungal growth [42]. This increased use of zinc supplements in COVID-19 therapy has paved a way for fungal infections.

6. Antibiotic use:

With the extensive use of broad-spectrum antibiotics, about 8% of patients developed secondary fungal infections during their hospital stay [5]. In one of the trials conducted on 17,534 admitted COVID-19 patients, of which 3.6% of patients developed secondary bacterial or fungal infections. The mortality among patients who developed secondary infections was 56.7%. The study analyzed the most commonly prescribed antibiotic and discovered that majority were from the “watch” (52.36%) and “reserve” categories (22.05%), and relatively fewer prescriptions were from the “access” category of WHO AWaRe classification (16.49%) potentially adding “fuel to the fire” of the already alarming antimicrobial resistance levels in India. According to the study, 10% of patients (70/640) received antifungals despite having no evidence of fungal illness, necessitating a concentrated intervention around antifungal rational use [43].

This widespread use of broad-spectrum medications from the "watch" and "reserve" categories would not only render drugs obsolete, but will also result in the emergence of highly drug-resistant bugs, which will be a nightmare for physicians. The normal bacterial flora guards against fungal colonization, most likely due to direct nutritional competition.

Even though the concept of invasive fungal growth is based on the increased colonisation seen following antibiotic therapy [44].

7. Cancer and transplantation:

Additional predisposing factors associated with mucormycosis in Indians, include malignancy (9.0%) and organ transplantation (7.7%) [45]. Hematological malignancy (HM) is a risk factor in 1–9% of mucormycosis patients in India [46]. SOT is a risk factor in 2.6–11 percent of mucormycosis cases in India, compared to 7–14 percent in the rest of the world [47]. The prevalence of mucormycosis in renal transplant recipients in India varies from 0.05% to 2.7% [48].

8. Use of iron chelators:

Some iron chelators can be significantly inhibitory to Rhizopus growth; however, others like deferoxamine may function as siderophores and actually deliver iron to fungal cells and promote growth. Patients receiving deferoxamine for iron overload related to hemodialysis have a significant risk for mucormycosis. It has an extremely high affinity for iron and can extract iron from transferrin and ferritin which is further used by rhizopus as an iron source by expressing an inducible receptor, which picks up deferoxamine-iron complexes and reduces ferric to ferrous iron during intracellular transport [49].

DIAGNOSIS:

A key reason why mucormycosis is difficult to diagnose is that it doesn't have characteristic symptoms. So, confirming the diagnosis needs both an alert clinician and a trained microbiologist. In a patient with hematological malignancy, a detailed history, physical examination, and imaging are required to diagnose suspected mucormycosis, and a pulmonary CT scan is advised for suspected pulmonary mucormycosis. In diabetic patients with facial pain, sinusitis, proptosis, ophthalmoplegia, cranial CT, MRI or endoscopy is strongly recommended to determine if sinusitis is present. The biopsy is strongly recommended if mucormycosis is suspected. Weekly CT scans are urgently suggested, especially in unstable patients, due to the rapid progression of mucormycosis [7]. In angioinvasive illness, histopathological analysis often indicates a primarily neutrophilic inflammatory response, with significant infarcts and angioinvasion [50]. The diagnosis by histopathological examination using 10% KOH and hematoxylin and eosin (H&E) stain is

shown in figure no. 3. A cranial MRI is indicated if the results show any involvement of the brain, sinuses and orbit [16].

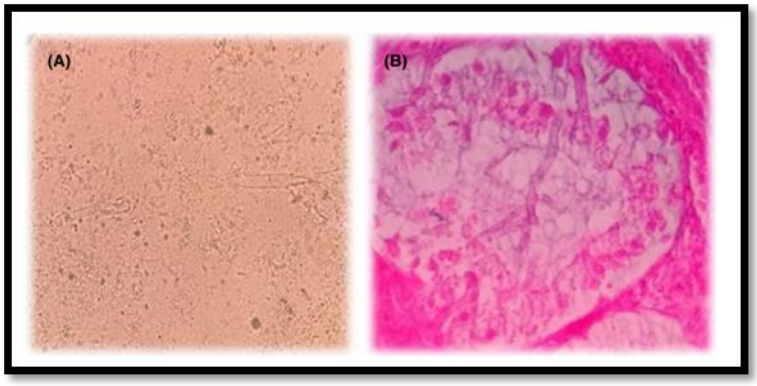

Figure No. 3: KOH examination (A) and hematoxylin and eosin (H&E) stain (B) showed abundant aseptate hyphae in the affected organs. Broad-angled, aseptate hyphae were diagnostic of mucormycosis [51]

TREATMENT:

Early diagnosis and reversal of predisposing variables are essential for successful treatment of mucormycosis [49]. However, the number of antifungal medications available for its treatment is limited. Liposomal Amphotericin B (LAMB) is still the first-line treatment for mucormycosis [52] whereas Posaconazole and Isavuconazole are preferred for salvage/de-escalation therapy. The improvement in the chest after amphotericin B therapy is shown in figure no. 4.

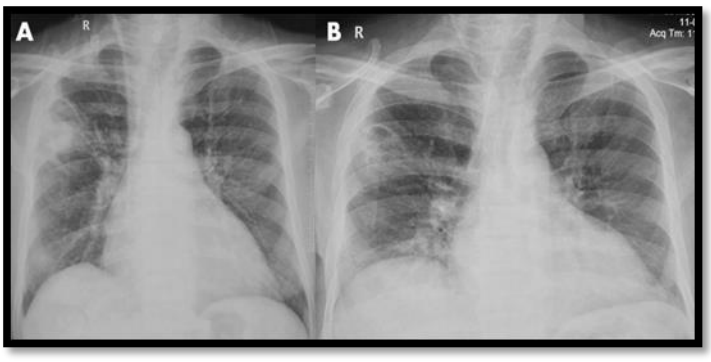

Figure No. 4: Chest radiograph performed at discharge **A** and after completing amphotericin therapy **B** showed significant resolution of the right upper zone cavity [40]

Amphotericin-B:

For mucormycosis, the therapeutic dose of amphotericin B deoxycholate (ABD) is 1 to 1.5 mg/kg/d. A study of 170 instances of sinus mucormycosis found that combining surgical debridement with ABD increased survival from 50% to 70% [49]. As shown in figure no. 5, the combination of Amphotericin B with Surgery significantly reduces the mortality rate compared to individual treatment with Amphotericin B or surgery.

Guidelines for mucormycosis published by the European Society for Clinical Microbiology and Infectious Diseases and the European Confederacy of Medical Mycology strongly favor LAMB 5 mg/kg over ABD [50].

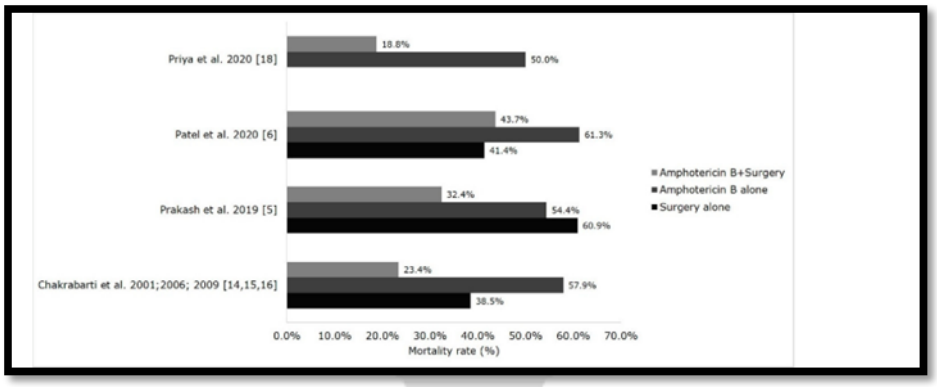

Figure No. 5: Modes of therapy and mortality rate in Indian population [8]

Amphotericin-B deoxycholate remains the anti-fungal treatment of choice to start, with its liposomal preparations preferred because of decreased nephrotoxicity.

Salvage therapy:

Triazoles like Isavuconazole and posaconazole are considered for salvage therapy against mucormycosis. Posaconazole is an alternative to amphotericin therapy for patients who are resistant to it. Posaconazole prophylaxis was found to be efficacious in high-risk individuals, such as neutropenic patients with graft versus host disease and patients with renal failure [17].

Medical treatment with Amphotericin B and surgical debridement are the two cornerstones of treatment. Once the diagnosis is confirmed, the diseased region should be surgically debrided as quickly as feasible. Although surgery alone has not been demonstrated to be curative, an intensive surgical approach has been shown to improve survival rates [53].

RECENT DEVELOPMENT:

IIT Hyderabad has developed an oral solution for black fungus which is extremely cost-effective. The first attempt was to fabricate nanofibrous oral tablets of Amphotericin B (AmB) for the potential cure of Leishmaniasis or Kala Azar which is devoid of nephrotoxicity. Since oral administration of AmB can minimize hospitalization costs and more significantly can aid patient compliance, several attempts to accomplish oral delivery of AmB have been made. It was found that synthesized AmB loaded gelatin nanofibers (1 mg/ml) showed its release up to 14 h [54].

MARKET SCENARIO:

The market scenario exacerbated in 2021 when the number of mucormycosis patients skyrocketed. Amphotericin B stocks ran out across India, likely pushing up fatality rates compared to pre-pandemic times. The ceiling price of Amphotericin B had been fixed by NPPA under the Drugs Prices Control Order, 2013. Its demand has increased in the wake of a surge in black fungus infections. The treatment cost been extremely high as a number of doses required per patient is also quite more. But it is the shortage of the drug that has emerged as the main impediment. Shortage of two raw materials-API and Synthetic lipids has hit the production cycle in India. Because synthetic lipids were primarily used in vaccine manufacture, there was a scarcity. Even when raw materials are available, production of the drug takes around 21 days, besides the time taken for the sterility test.

CONCLUSION:

The prevalence of mucormycosis in India during COVID-19 treatment appears to increase and contribute to significant morbidity and mortality. During the second wave of Covid-19, the market analysis revealed a jump in demand for pharmaceuticals used to treat mucormycosis, and how an epidemic led to a marked expansion of drugs including Amphotericin B, Isavuconazole, and Posaconazole, which enhanced the mucormycosis market. A statistically increased prevalence of mucormycosis is linked to the use of steroids frequently, poorly controlled diabetes, and oxygen supply pollution in ventilators. There's still a lot to learn about the triple threat that has formed as a result of the pandemic, but having better knowledge will allow us to monitor the blood glucose levels of diabetic patients and avoid using corticosteroids and broad-spectrum antibiotics. Antifungal medication combined with surgical debridement may enhance these patients' chances of survival. In the

future, oral tablets of Amphotericin B created by IIT Hyderabad should be explored for treating mucormycosis because they are both cost-effective and patient-friendly. In an epidemic crisis, preparations for drug supply must be considered, as this will aid in providing better treatment and lowering mortality rates.

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