Review article

EFFECT OF MUCORMYCOSIS ON POST COVID-19 PATIENTS

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ABSTRACT

The study was carried out in 2021, The aim of this study is to evaluate the prevalence, pathogenesis and management of mucormycosis in post covid-19 patients. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been sweeping across the globe. Based on a retrospective analysis of SARS and influenza data from China and worldwide, we surmise that the fungal co-infections associated with global COVID-19 might be missed or misdiagnosed. Although there are few publications, COVID-19 patients, especially severely ill or immunocompromised, have a higher probability of suffering from invasive mycoses.

Increasing number of patients with COVID-19-associated mucormycosis have been reported, especially from India recently. We have described a patient with COVID-19-associated mucormycosis and, searched and analyzed current medical literature to delineate the characteristics of COVID-19-associated mucormycosis. Method: We reported a patient developed mucormycosis during post-COVID period. We searched literature to describe the incidence, clinical features, and outcomes of COVID-19-associated mucormycosis. Demographic features, risk factors, clinical features, diagnostic methods, treatment and outcome were analyzed. Results: We describe a person, hospitalized due to severe COVID-19 pneumonia. He was given longterm, high doses of systemic steroids. He developed maxillo-fascial mucormycosis and died of sepsis. Conclusions: Steroid use, diabetes, environmental conditions, excessive use of antibiotics, and hypoxia are main risk factors. Despite medical and surgical treatment, mortality rate is high. A multidisciplinary approach is essential to improve the conditions facilitating the emergence of COVID-19-associated mucormycosis. We suggest it is prudent to assess the risk factors, the types of invasive mycosis, the strengths and limitations of diagnostic methods, clinical settings, and the need for standard or individualized treatment in COVID-19 patients. Amphotericin B have become the standard treatment for mucormycosis.

Keywords: COVID-19 Coronavirus, Mucormycosis, Mucor, Fungal infections.

1.INTRODUCTION

During the year 2021, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is associated with a wide clinical spectrum of Coronavirus Disease 2019 (COVID19) that ranges from being asymptomatic to severe disease requiring intensive care unit (ICU) admission. The rate of admission to ICU is about 5% of all COVID-19 patients. Severe COVID-19 pneumonia is associated with immune dysregulation and cytokine syndrome leading to the increased use of immunomodulators. Emerging fungal infections such as aspergillosis were described in critically ill patients treated with steroids. The mortality rate of SARS-CoV-2 infection in critically ill patients co-infected with aspergillosis was high. Mucormycosis is a life-threatening infection caused by fungi of the order Mucorales. Recent re-classification has abolished the class Zygomycetes and placed the order Mucorales in the subphylum Mucormycotina . Therefore, we refer to infection caused by Mucorales as mucormycosis rather than zygomycosis. Mucormycosis typically occurs in patients with diabetes mellitus, organ or hematopoietic stem cell transplantation (HSCT), neutropenia, or malignancy. The incidence of mucormycosis appears to be increasing, based on data from cancer centers in the United States and Europe and PubMed publications. Furthermore, a recent, comprehensive, population-based epidemiology study found a near doubling of the frequency of mucormycosis cases throughout France over a 10-year period (1997–2006). For decades, the mortality rate of mucormycosis has remained ≥40% despite aggressive surgical and antifungal therapy, in patients with hematologic malignancy or HSCT, mortality rates exceed 65% and 90%. However, recent translational research, funded by the US National Institutes of Health and by the pharmaceutical industry, has resulted in several new treatment strategies for mucormycosis, raising the possibility of improving outcomes based on superior medical therapy. Most cases of mucormycosis result from inhalation of fungal sporangiospores that have been released in the air or from direct inoculation of organisms into disrupted skin or gastrointestinal tract mucosa. Seasonal variations affect the incidence of mucormycosis, with most infections occurring from August to November. In a recent study, presenting the epidemiology of mucormycosis in Australia, trauma patients were more often infected with uncommon, non-Rhizopus spp. the patients infected with Apophysomyces spp. or Saksenaea spp. were all immunocompetent, had predominantly acquired infection through trauma, and had infection frequently localized to the skin, soft tissues, and bones.

2. Manifestation of Mucormycosis

Mucormycosis symptoms vary depending on where the fungus develops in the body. Symptoms of rhinocerebral mucormycosis include black sores on the nasal bridge, fever, one-sided face edema, headache, and nasal congestion, whereas the symptoms of cutaneous mucormycosis are swelling around the wound, pain, and excessive redness. By contrast, the symptoms of pulmonary mucormycosis include breathlessness, chest pain, coughing, and fever. Finally, the symptoms of gastrointestinal mucormycosis include stomach pain, stomach bleeding, and nausea and vomiting. Because disseminated mucormycosis develops in patients who have been admitted to the hospital for other diseases, determining which symptoms are caused by mucormycosis can be difficult. Eventually such patients may develop mental status changes that may lead to coma. Because some of the symptoms of mucormycosis and COVID-19 are similar, physicians may have difficulty determining whether an individual is infected with a fungus or with COVID-19. Furthermore, certain patients may have COVID-19 along with a fungal infection.

3. Epidemiology

According to recent data, the number of reported cases of mucormycosis has increased significantly. For example, the incidence of mucormycosis has increased dramatically in major transplant facilities, with the number of patients more than doubling in 15 years. Among autopsied individuals who had leukemia, the incidence of mucormycosis reached 8% in high-risk individuals, with diabetes mellitus reported in 54–76% of cases and diabetic ketoacidosis in 8–22%. In north India, individuals who had diabetes mellitus exhibited a 0.16–1.72% occurrence of mucormycosis. Mucormycosis revealed diabetes in 24% of patients in south India, 40% in western India, and 43% in north India, reflecting a lack of routine health checkups among Indian people. In India, 1–9% of mucormycosis patients have a hematological malignancy, compared with 38–62% in the United States and Europe. The frequency of confirmed mucormycosis was 1.4% among 781 acute leukemia patients studied in north India. In a study of acute myeloid leukemia patients in south India, the prevalence of verified mucormycosis cases was 0.9%. In India, solid-organ transplantation is a risk factor in 2.6–11% of mucormycosis cases, compared with 7–14% globally. Furthermore, in India, mucormycosis occurs in from 0.05% to 2.7% of renal transplant patients, versus 0.04–0.05% globally . According to many investigations, mucormycosis is found in 0.56–1.52% of kidney transplant recipients in south India. Steroid treatment, chronic obstructive pulmonary disease, chronic renal illness, and pulmonary

tuberculosis are all risk factors for mucormycosis in India, where chronic kidney disease has emerged as a new risk factor for mucormycosis. According to Indian studies, 9–32% of mucormycosis patients have chronic kidney disease . Likewise, chronic obstructive pulmonary disease and pulmonary tuberculosis have been reported in 7–46% of individuals who had mucormycosis. Low birth weight babies, chronic alcoholism, liver diseases, renal failure, intravenous drug use, malnutrition, and acquired immunodeficiency syndrome are all factors associated with mucormycosis. Mucormycosis is exceedingly uncommon in HIV-positive individuals. Only two individuals developed mucormycosis in a retrospective analysis of 1630 autopsy of AIDS patients who died between 1984–2002. The most prevalent comorbidities were the usage of corticosteroid (25%), neutropenia (29.7%), and intravenous drug use (IVDU 50%). Individuals with a record of intravenous drug use who experienced mucormycosis are more likely to present with localized cerebral inflammation . In Indian research published in 2019, chronic renal illness (8.9%) and post-pulmonary TB (6.9%) were identified as rising risk factors.

TAXONOMY OF MUCOR :

Kingdom	Fungi
Phylum	Mucormycotina
Order	Mucorales
Family	Mucoraceae
Genera	mucor

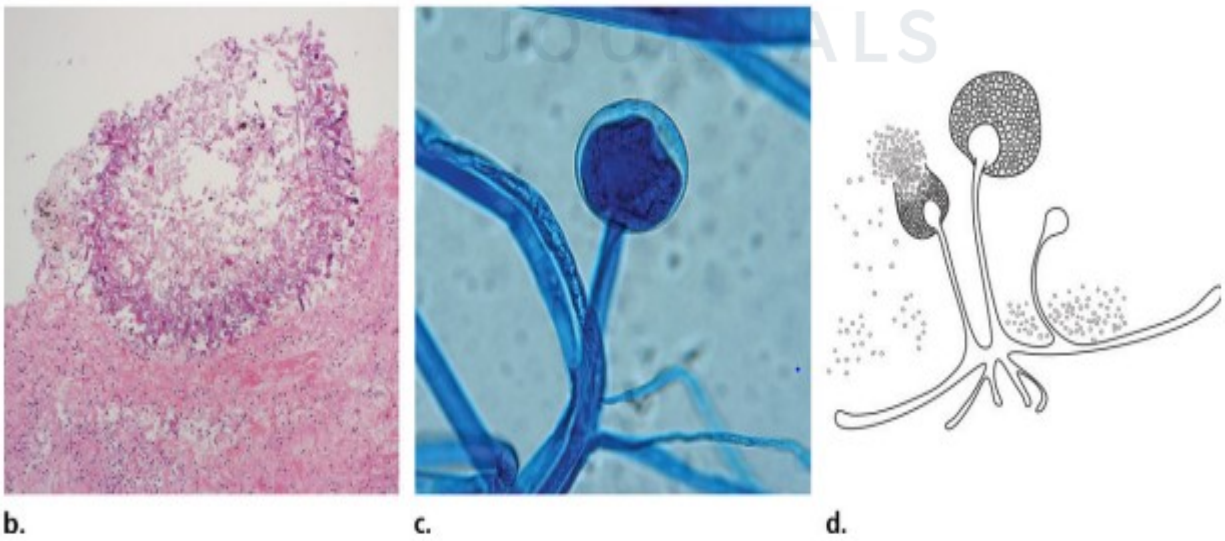
TYPES OF MUCORMYCOSIS

- Rhinocerebral Mucormycosis
- Pulmonary Mucormycosis
- CutaneousbMucormycosis
- Gastrointestinal Mucormycosis
- Disseminated Mucormycosis

STRUCTURE OF MUCOR:

a.

Fig 1. (a) Macroscopic photograph shows Mucor sporangia growing on old bread. (b) Photomicrograph of a fungus ball obtained from lung tissue shows multiple clustered hyphae and sporangia. (c) High-power photomicrograph shows a spherical structure called the sporangium. The wall of the sporangium dissolves on maturity, exposing the spores. (d) Drawing of a sporangium at the tip of a hyphal stalk.



(Source: radiographics.rsna.org)

REVIEW OF LITERATURE

The relevant literature available concerning **"EFFECT OF MUCORMYCOSIS ON POST COVID-19 PATIENTS"** have been collected and presented in this chapter.

1. A Bras Dermatol (2017) reported that Cutaneous mucormycosis is an emerging fungal infection caused by opportunistic fungi of the phylum Glomero-mycota.
2. Ahmet Dilek a,b , Resat Ozaras c , Sevket Ozkaya d,e , Mustafa Sunbul f , Elif Itir Sen g , Hakan Leblebicioglu h,: COVID-19-associated mucormycosis: Case report and systematic review.

   Increasing number of patients with COVID-19-associated mucormycosis have been reported, especially from India recently. We have described a patient with COVID-19-associated mucormycosis and, searched and analyzed current medical literature to delineate the characteristics of COVID-19-associated mucormycosis
3. Ashraf S. Ibrahim (2021) studied Pathogenesis of Mucormycosis.
4. Benoit Pilmis(2018) studied in detail the Recent advances in understanding mucormycosis.
5. Brad Spellberg, (2005) studied about the Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management.
6. Iyer Mahalaxmi (2021) published a journal on Mucormycosis: An opportunistic pathogen during COVID-19.
7. Jafar A (2021) studied COVID-19 and mucormycosis superinfection: the perfect storm.

   In this review, included most recent reported case reports and case-series of mucormycosis among patients with COVID-19 and describe the clinical features and outcome. Many of the mucormycosis reports were eported from India, especially in COVID-19 patients who were treated and recovered patients. The most commonly reported infection sites were rhino-orbital/rhino-cerebral mucormycosis. Those patients were diabetic and had corticosteroids therapy for controlling the severity of COVID-19, leading to a higher fatality in such cases and complicating the pandemic scenario. The triad of severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), corticosteroid use and uncontrolled diabetes mellitus have been evident for signifcant increase in the incidence of

angioinvasive maxillofacial mucormycosis. In addition, the presence of spores and other factors might play a role as well.

8. Lav Selarka(2021) studied in detail about Mucormycosis and COVID-19: An epidemic within a pandemic in India.

   This prospective, observational, multi-centre study included 47 consecutive patients with mucormycosis, diagnosed during their course of COVID-19 illness, between January 3 and March 27, 2021. Data regarding demography, underlying medical conditions, COVID-19 illness and treatment were collected. Clinical presentations of mucormycosis, imaging and biochemical characteristics and outcome were recorded.
9. S Sharma (2021) published a journal on Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum.

   A prospective observational study was conducted at a tertiary care centre over four months, involving all patients with mucormycosis of the paranasal sinuses suffering from or having a history of coronavirus disease infection. Twenty-three patients presented with mucormycosis, all had an association with coronavirus disease 2019. The ethmoids (100 per cent) were the most common sinuses affected. Intra-orbital extension was seen in 43.47 per cent of cases, while intracranial extension was only seen in 8.69 per cent. Diabetes mellitus was present in 21 of 23 cases, and was uncontrolled in 12 cases. All patients had a history of steroid use during their coronavirus treatment.

MATERIALS AND METHODS

Search strategies and study selection Literature search was performed in PubMed, PUBMED, Web of Science, The literature was searched using keywords of [(COVID 19 OR Coronavirus OR corona) AND (mucormycosis OR mucor)].

1.Inclusion criteria

Case reports, case series, and observational studies describing the incidence, clinical features, and outcomes of mucormycosis developed in COVID-19 patients were included in the systematic review. Case reports without clinical and laboratory features were excluded. Demographic features, risk factors, clinical features, diagnostic methods, treatment and outcome were analyzed.

2.Case definition

Mucormycosis cases were classified as “possible”, “probable” or “proven” according to the recently published guideline of “Code Mucor: Guidelines for the Diagnosis, Staging and Management of Rhino-OrbitoCerebral Mucormycosis in the Setting of COVID-19”. This guideline describes rhino-orbito-cerebral mucormycosis. For the patients with involvement other than these, the criterion of “probable” was modified to include organ-specific endoscopic procedures and MRI or CT imaging studies. In brief, among patients with proven COVID-19 infections, presence of typical clinical mucormycosis findings is described as “possible”; in addition to these, presence of nasal/pulmonary/gastrointestinal endoscopic or MRI/CT findings compatible with mucormycosis is described as “probable”; and in addition to these, if mucormycosis is proven by microbiologic, histologic, and molecular methods, it is classified as “proven”. All “probable” and “proven” cases were included into the review.

OBSERVATION

1.Mucormycosis mode of action in normal individuals:

Mucormycosis is caused by the inhalation of its filamentous (hyphal form) fungi, especially in patients who have undergone weakness in the arsenal of immune defense. The characteristic phenotype of this disease is the growth of hyphae in and around the blood vessels, leading to lifethreatening scenarios in severely immunocompromised patients. Once the fungal spores invade the human system, the hyphae intrude on the blood vessels, resulting in tissue infarction, necrosis and thrombosis. Mucormycosis occurs in the host by two steps: 1) by evading the immune system and surviving inside the host cell, 2) perturbation of the immune system further damaging the host cell. In immunocompromised patients, iron is abundantly released via sequestering proteins which creates a favorable environment for the growth of fungi inside the human body. Also, Mucorales fungi consume iron using high-affinity iron permease and transport iron to development inside the host cell. The virulence factors of the pathogen play a key role to accomplish the damage. Spore coat (CotH) protein which is present on the spore surface of the Mucorales is responsible for penetrating, disrupting and damaging the immune cells. The epithelial cells are the first line of contact to fungal pathogens, especially the mucoralean fungi damaging the epithelial cell via increased signaling of platelet-derived growth factor receptor B (PDGFRB) provides the proper growth factors to the fungi. The neutrophils are the first line of defense against these fungi, as these are an important part of the innate immune system and regulate the adaptive immune system. In diabetic or

steroid use patients due to ketoacidosis or hyperglycemic conditions, the chemotactic factors released by neutrophils decrease thereby increasing the fungal hyphae in human hosts. The Mucorales, after entering the host cell produces Mucorales-specific T-cells which generates interleukins (IL-4, IL-10 and IL-17) and IFN-γ. These pro-inflammatory cytokines further stimulate CD4+ T cells and damage the host cell. Also, the fungal hyphae reduce the release of various immunomodulatory molecules such as RANTES (regulated upon activation, normal T-cell expressed and secreted) and IFN-γ, which are secreted by NK cells which appears in the early stage of infection. These key findings explain the susceptibility of immunocompromised patients to mucormycosis and its possible mechanism of action inside the host cell.

2.COVID-19 and mucormycosis:

A tangled relation The advent of COVID-19 has sprung upon the world myriad of conditions and complications. Mucormycosis is an another milestone added in COVID-19, that has emerged as a deadly complication associated with COVID-19. In March 2021, 41 cases of COVID-19 associated mucormycosis has been reported worldwide and 70% were from India. There is a surge in these cases amidst the second wave in India. There have been 2245 cases and 120 deaths from the infection in Maharashtra state. As of June 5, 2021, Rajasthan reported 2651 cases and 85 deaths and Telangana reports around 50 cases daily. In Tamil Nadu, till June 9, 2021, total mucormycosis reported being to be 1196 . The mucormycosis stemming from COVID-19 patients has been more commonly observed in patients with a history of diabetes mellitus and 95% of individuals with severe or critical COVID-19. In addition to this, a two-month-old heart transplant patient developed mucormycosis three months after the COVID-19 diagnosis. This was of the cutaneous type as the old intravascular device location and despite aggressive treatment, the patient had died . This evidence indicates that transplant patients need more vigilant care in the clinical setting while managing COVID-19 as these patients are already predisposed to mucormycosis. Similarly, a patient with acute myeloid leukemia (AML) also suffered mucormycosis after the COVID-19 infection. Although these factors such as diabetes, organ transplantation and hematological factors are commonly linked to mucormycosis, it is evident that COVID-19 infection also acts as a trigger in these situations. In addition, it has also been observed that people with no history of any underlying condition can also be diagnosed with mucormycosis post-COVID-19 infection. There are many plausible explanations for the occurrence of mucormycosis post-COVID-19 infection. COVID-19 patients exhibit a wide array of pulmonary

changes which may be a focal point for fungal initiation. Moreover, COVID-19 is also associated with immune disfunction preventing the polymorphonuclear phagocytes from attacking the fungal spores upon entry. Patients with severe COVID-19 also require a prolonged hospital stay and mechanical ventilation the occurrence of fungal spores in this equipment could also contribute to mucormycosis in these individuals. The immunosuppressants and corticosteroid medications that are warranted in COVID-19 can contribute significantly to the occurrence of mucormycosis. Further, in addition to hyperglycemia, COVID-19 also contributes to changes in iron metabolism. High ferritin levels have been observed in COVID-19, the high iron concentrations release reactive oxygen species while damaging the nearby tissue. The cytokines released during COVID-19 further increases intracellular iron and leakage of iron into the circulation, posing as a risk factor for the development of mucormycosis. Although the diagnosis of mucormycosis is mainly made by observing fungus in biopsies and culturing the tissue, waiting for the cultures in the dire COVID-19 situation may be impractical as the progression of mucormycosis is speedy. Also, other therapeutic options besides reversal of underlying cause must be implemented as the reversal of these conditions may not be possible while treatment is ongoing for COVID-19. This is especially true due to the need to use high doses of steroids for the treatment of COVID-19. In this condition, it is evident that the use of antibiotics and steroids may be dangerous for some patients as they may trigger the onset of these life-threatening fungal infections. It is extremely important for the doctors treating patients with COVID-19 to be mindful of patients with underlying illnesses and prescribed steroids or immunosuppressants. Despite the tremendous burden on the healthcare system due to the overwhelming increase in cases, more vigilance is required in utilizing preventive measures for this condition. Also, it is important to periodically check the air in the hospital wards and the oxygen therapy machinery for spores. In addition, recovered patients should also be advised to stay indoors for few weeks to build up their immunity and follow-up studies to prevent any adverse complications. Since it’s important that care should be taken in disposal of solid waste of COVID-19 patients, similar measures must be undertaken for individuals with the infection. Moreover, there is an urgent need to develop prompt diagnostic measures to manage mucormycosis in time. The proper management of mucormycosis must be prioritized to prevent more COVID-19 related deaths.

3.Possible role of action of mucormycosis among COVID-19 patients :

The symptoms of COVID-19 includes a rise in body temperature, osmolarity, hypoxia and breathlessness. The COVID-19 recovered patients of late have been distressed with a new infection called mucormycosis disease. This fungal disease could easily invade the sinus and lungs, making its way to intra-orbital and intracranial regions of the body. The main symptoms of COVID-19 create a perfect environment for the growth and development of Mucorales inside the human body. Hosts susceptible to mucormycosis include diabetics, those on systemic corticosteroid use, patients with neutropenia and hematologic malignancies, stem cell transplant patients and immunocompromised individuals. Reports suggest that diabetic patients are more prone to acquire COVID-19 accompanied by mucormycosis infection The potential mechanism by which diabetes increases COVID-19 morbidity, and mortality is a) reduced viral clearance, b) decrease in T-cell function, c) high cytokine storm, d) immune-suppression. Hyperglycemia worsens the cytokine storm by disrupting endothelial cells leading to multi-organ damage in COVID-19 patients. During diabetic ketoacidosis, the acidic environment and increase in the levels of free ferric ions support the growth of Mucorales. These circumstances support the invasion and successful attachment of the hyphae from the Mucorales inside the body. Individuals with chronic diabetes accompanied with foot ulcers are prone to this infection as any injured skin tissue is an easy entry route for this fungus. Further, treatment for COVID-19 is still preliminary, and to combat the effect of SARS-CoV-2 infection, patients are given heavy doses of steroids (corticosteroids), as it reduces the inflammation in the lungs and might also curb the damages that had happened in the body due to the cytokine storm. Meanwhile patients affected with this new strain of COVID-19 are mostly treated with heavy steroids, extreme use of oxygen masks and ventilators which makes these patients more susceptible to mucormycosis. Steroids reduce both inflammation and the activity of the immune system, where the production of white blood cells (WBCs) and T-helper cells are decreased, making it easy for any foreign substances to invade and completely corrode the immune system in the host cell. Also, these steroids could trigger the uncontrolled release of sugar, which also enables the Mucorales to grow, multiply and invade at a rapid rate (“What patients with diabetes, cancer and kidney disorders need to know about black fungus,”). Only a few case reports have been published regarding the impact of mucormycosis on COVID-19 affected patients. Hence, these possible mechanisms have been listed based on the points and suggestions provided by various doctors and researchers, where the above-explained reasons may be

potential factors for the occurrence of mucormycosis among COVID-19 recovered or infected patients.

TREATMENT

The successful treatment of mucormycosis requires four steps: 1) early diagnosis; 2) reversal of underlying predisposing risk factors, if possible; 3) surgical debridement where applicable; and 4) prompt antifungal therapy.

Early Diagnosis

A recent study from Chamilos et al. quantified the benefit of early initiation of polyene antifungal therapy. They reported that if treatment was initiated within 5 days of diagnosis of mucormycosis, survival was markedly improved compared to initiation of polyene therapy at ≥6 days after diagnosis (83% vs 49% survival). Hence, establishing an early diagnosis of mucormycosis is critical to enable early initiation of active antifungal therapy. The development of other diagnostic methods is a major unmet need for this infection. Development of quantitative polymerase chain reaction systems is a promising area of ongoing research to enable more rapid diagnosis. The most common finding by CT scanning of patients with rhino-orbital-cerebral disease is simply sinusitis, so absence of deeper infection by CT scan does not rule out mucormycosis . MRIs are more sensitive than CT scans for detecting orbital and central nervous system (CNS) involvement. CT scans are useful for early detection of pulmonary mucormycosis, particularly in patients with cancer. By logistic regression, pulmonary mucormycosis in patients with cancer could be distinguished from aspergillosis on the basis of sinusitis, presence of multiple (≥10) nodules by CT scan, and pleural effusion.

Reversal of Underlying Disease

It is critical to reverse/prevent underlying defects in host defense when treating patients with mucormycosis. Immunosuppressive medications, particularly corticosteroids, should be dose reduced or stopped if at all possible. Aggressive management to rapidly restore euglycemia and normal acidbase status is critical in diabetic patients in ketoacidosis. Administration of iron should be avoided, because it exacerbates the severity of infection in animal models of mucormycosis. For the same reason, it may be advisable to minimize blood transfusions, if feasible.

Surgical Management

Blood vessel thrombosis and resulting tissue necrosis during mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of necrotic tissues may be critical for complete eradication of mucormycosis. In a recent study, surgery was found to be an independent variable by logistic regression for favorable outcome in patients with mucormycosis. Furthermore, in multiple case series, patients who did not undergo surgical debridement of mucormycosis had a far higher mortality rate than patients who underwent surgery. Although there is potential selection bias in these case series, as patients who did not undergo surgery likely differed in disease severity or comorbidities from those who did, these data support the concept that surgical debridement is necessary to optimize cure rates. The extent and timing of surgical debridement necessary to maximize outcomes of mucormycosis has never been defined. Data from a recent retrospective review of patients with rhino-orbital-cerebral mucormycosis support the use of intraoperative frozen sections to delineate the margins of infected tissues so that uninvolved tissues can be spared from debridement. The use of calcofluor fluorescence microscopy has also been reported to increase the sensitivity of frozen sections for guiding extent of surgical revision.

Antifungal Therapy

First-Line Monotherapy Options In general, primary antifungal therapy for mucormycosis should be based on a polyene, if possible. Although amphotericin B deoxycholate (AmB) was the cornerstone of mucormycosis therapy for decades, lipid formulations of AmB are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time than AmB . Furthermore, treatment of mucormycosis with liposomal amphotericin B (LAmB) was associated with a 67% survival rate, compared to 39% survival when patients were treated with AmB (p=0.02). Multiple other, more recent case series also found initial therapy with LAmB to be substantially more effective than other options. Therefore, most experts now prefer to use lipid polyenes rather than AmB for the treatment of mucormycosis. Available data indicate advantages of LAmB over amphotericin B lipid complex (ABLC) for the treatment 424 Curr Infect Dis Rep (2010) of CNS mucormycosis. For example, LAmB levels achieved in rabbit brain were fivefold above ABLC levels. Furthermore, while similarly effective in neutropenic mice, LAmB was markedly superior to ABLC in diabetic ketoacidotic (DKA) mice infected with Rhizopus oryzae, primarily because of superior clearance of fungus from the brain [38]. These animal studies are

complemented by a recent, relatively small retrospective case series, in which the outcomes of patients with rhino-orbital-cerebral mucormycosis were found to be worse when ABLC was used as initial therapy versus AmB or LAmB. In contrast, a recent murine study found that ABLC achieves superior lung levels than LAmB, resulting in superior clearance of fungus from the lungs. When a higher dose of LAmB was used than ABLC, the efficacy was similar. No clinical studies are available yet to validate these intriguing murine data. In the absence of definitive data on dose selection, 5– 7.5 mg/kg/d of lipid polyenes are reasonable for most cases of mucormycosis. A recent randomized study of 339 patients with various mold infections found no clinical benefit of LAmB dosed at 10 mg/kg/d versus 3 mg/kg/d [40]. However, there were only five total cases of mucormycosis in the study, none of which involved the CNS. Given the low CNS penetration of polyenes, some experts prefer dose escalation to 10 mg/kg/d of LAmB for CNS mucormycosis. Higher doses of LAmB do not result in pharmacokinetic advantage compared to 10 mg/kg/d. Fluconazole, voriconazole, and itraconazole do not have reliable activity against mucormycosis. The reported in vitro minimum inhibitory concentration for 90% of organisms (MIC90) of posaconazole against the Mucormycotina has ranged from 1 μg/mL to ≥4 μg/mL. However, in patients with febrile neutropenia or invasive fungal infections, posaconazole dosed at 400 mg twice daily resulted in serum levels less than 1 μg/mL, with considerable variability. These data raise concerns about the reliability of achieving adequate in vivo levels of posaconazole to treat mucormycosis. Furthermore, posaconazole is relatively ineffective for the treatment of mucormycosis in pre-clinical animal models. The efficacy of posaconazole as a treatment option is further called into question by reports of mucormycosis developing as a breakthrough infection while on posaconazole prophylaxis. Thus, posaconazole cannot be recommended as a first-line treatment for mucormycosis. In contrast, van Burik et al. reported 60% response rates (45% partial response, 15% complete response) for salvage therapy in patients with mucormycosis who were refractory to or intolerant of polyenes. Greenberg et al. reported similar results. Hence, posaconazole is an option for salvage therapy for these infections.

Salvage Therapy

Posaconazole or deferasirox are reasonable salvage options for patients with mucormycosis refractory to or intolerant of polyene therapy. Substantially more clinical data are available for posaconazole in this setting. Posaconazole appears to be quite safe despite dosing for months to years of administration.

Mucormycosis, although relatively rare, poses an important burden on immunocompromised patients, due to its persistently high mortality. The development of newer, more effective, immunosuppressive medications has been associated with an increase of its incidence. Diabetics are also susceptible to this potentially lethal disease, especially in developing countries. There are several studies on its pathogenesis, but there are still many questions to be answered. The diagnosis and treatment of mucormycosis remain a challenge. The clinical presentation is nonspecific, and, when it becomes apparent that the patient most probably has mucormycosis, it is often too late to administer effective treatment. Early diagnosis is thus crucial and is the main target of current research. Direct examination, culture and histopathology are the cornerstones of diagnosing mucormycosis, but they are time consuming and lack sensitivity. Newer molecular diagnostic techniques, such as in situ hybridization and PCR, offer an alternative which may lead to earlier diagnosis and prompt initiation of treatment. The management of mucormycosis is multimodal, including reversal of underlying risk factors, administration of antifungal agents, surgical intervention and various adjunctive therapies. Timely and adequately dosed antifungal therapy is necessary. Amphotericin B and posaconazole are the most often used medications. Isavuconazole is a new triazole, with activity against the agents of mucormycosis, but it does not seem to offer an increased chance of survival, compared to older treatments. Immunologic and metabolomic profiling of the host, targeted immunotherapy and reversal of tissue hypoxia, may evolve in the future, leading to a better treatment of this devastating disease.

RESULT

1.Depletion of organs due to mucormycosis:

Mucormycosis can frequently infect the sinuses, brain or lungs but it has been said that it can also the impact on oral cavity, gastrointestinal tract, skin and other organs. The infection of mucormycosis could result in the following outcomes in different organs 1) when infected in the sinusitis, it blocks the nasal cavity leading to blackish or bloody discharge; 2) Face-local pain on cheekbone, one-sided facial pain or numbness; 3) Oral cavity-loosening of teeth or jaw; 4) Eye-blurred/ double vision, vision loss; 5) Skin-thrombosis or necrotic skin lesion; 6) Lungs-chest pain, worsening of respiratory symptoms. However, in COVID-19 affected patients, mostly it affects the eye, oral region and brain.

1.1 Eye

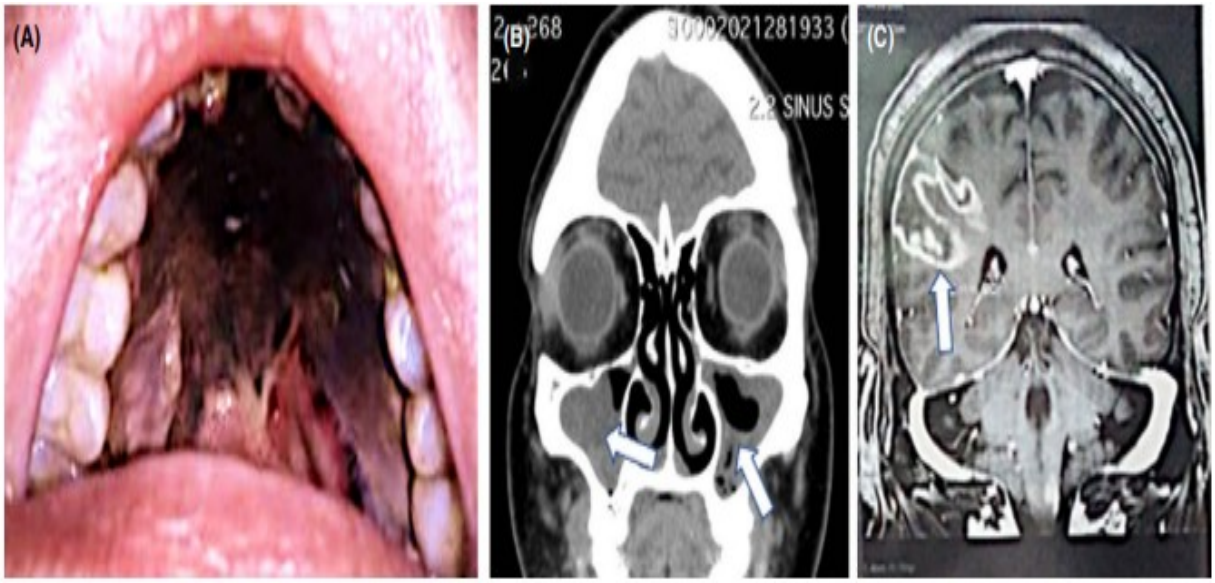
The mucormycosis infection classically starts its journey inside the human body in the nasal or maxillary sinus and spreads to sphenoid or ethmoid sinus. After which it intrudes the orbit via ethmoid foramina or nasolacrimal duct or by splitting lamina papyracea. The lesion in the eye occurs due to the angioinvasion of the germinated hyphae resulting in dry gangrene. Whereas when the angioinvasion occurs via cavernous sinus thrombosis/internal carotid artery results in cerebral infarction, mycotic abscesses or aneurysms and hematogenous dissemination. When the blood vessel necrosis occurs in the ophthalmic artery it might lead to blindness, cranial nerve palsies and other motor and sensory deficits.

1.2 Mouth

Mucormycosis occurs in the oral cavity mainly due to spread of spores through inhalation, open oral wounds, ulceration or an extraction socket in the mouth, particularly in the patients who are immunocompromised. Diagnosis can be made based on the appearance of necrotic lesions in the form of pressure sores in the orbital-nasal region, the palate or the floor of the mouth. The infection of mucormycosis especially in the maxillofacial regions spreads to regions such as the oral cavity, maxilla, palate, nose, paranasal sinuses and finally into CNS. Angioinvasion of Mucorales and its spores into the blood vessels leads to the thrombus formation, which causes progressive necrosis of associated hard and soft tissues.

1.3 Brain

The manifestation of mucormycosis in the CNS mainly questions the survival rate and proper functioning of the organs in the infected individual. After the entry of the fungus, the invasion occurs either via hematogenous spread or by direct cranial dispersion from the paranasal sinuses. Patients who have diabetes mellitus as a major co-morbidity for mucormycosis, the CNS becomes the third most common site of infection. The fungal hypha develops in the internal elastic lamina and spreads to the arterial lumen, eradicating intravascular thrombosis. Vascular occlusion leading to cerebral infarction and hemorrhagic necrosis, even before hyphal invasion in brain tissue. Hyphal invasion of the necrotic brain parenchyma occurs in advanced CNS mucormycosis and might lead to death. Hence, the growing piece of evidence shows that it is important to have options open to diagnose this disease in different dimensions. It has several sites of infection mainly attacking the immune system and causing infection in individuals.



(Source: SELARKA et al)

(Fig.2). Clinical and radiological features of a 61-year-old female patient with poorly controlled diabetes mellitus (type 2) who was diagnosed with moderate-severity COVID-19 and invasive rhino-orbital-cerebral mucormycosis. The patient had received systemic corticosteroids and broad-spectrum antibiotics for the management of severe COVID-19 pneumonia. She eventually succumbed to the disease. On presentation, she had complete right-sided ptosis, proptosis and complex ophthalmoplegia suggestive of orbital apex syndrome. There was also right peri-orbital and hemifacial swelling and tenderness. The patient had dysphagia which necessitated the insertion of a nasogastric tube. (A) Examination of the oral cavity revealed the presence of black necrotic tissue involving the palate with pharyngeal extension consistent with an eschar. (B) Coronal CT scan of paranasal sinuses showing bilateral right more than left-sided opacification of the maxillary sinuses with poor aeration. Gadolinium-enhanced T1-weighted axial magnetic resonance imaging demonstrates the presence of a heterogeneously enhancing intra-orbital lesion with contiguous involvement of the right cavernous sinus. (C) Gadolinium-enhanced T1- weighted coronal magnetic resonance imaging of the brain demonstrates the presence of a right-sided ring-enhancing lesion suggestive of a fungal abscess.

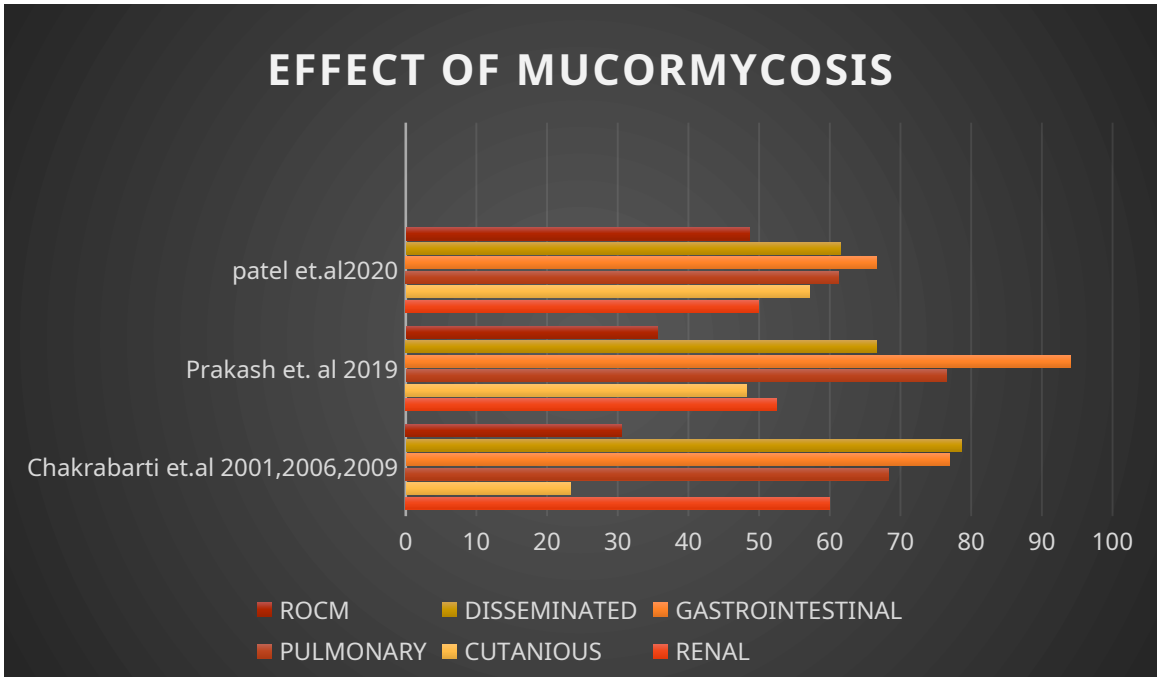
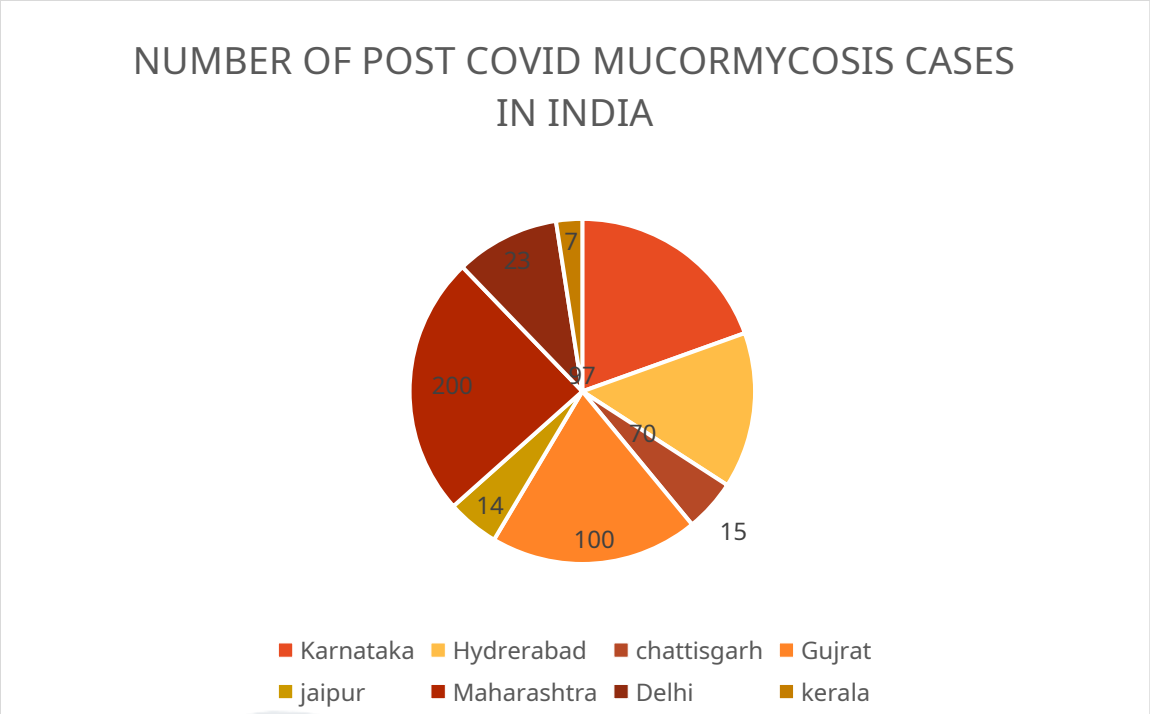


Fig.3. source: Epidemiology of Mucormycosis in India

Type of mucormycosis	Chakrabarti et.al.2001,2006,2009	Prakash et.al 2019	Patel et.al.2020
Renal	60.0 %	52.5 %	50.0 %
Cutanious	23.3 %	48.3 %	57.1 %
Pulmanary	68.4 %	76.5 %	61.3 %
Gastrointestinal	76.9 %	94.1 %	66.7 %
Disseminated	78.6 %	66.7 %	61.5 %
ROCM	30.6 %	35.6 %	48.6 %



(fig.4.)-Number of Post covid mucormycosis cases in India.

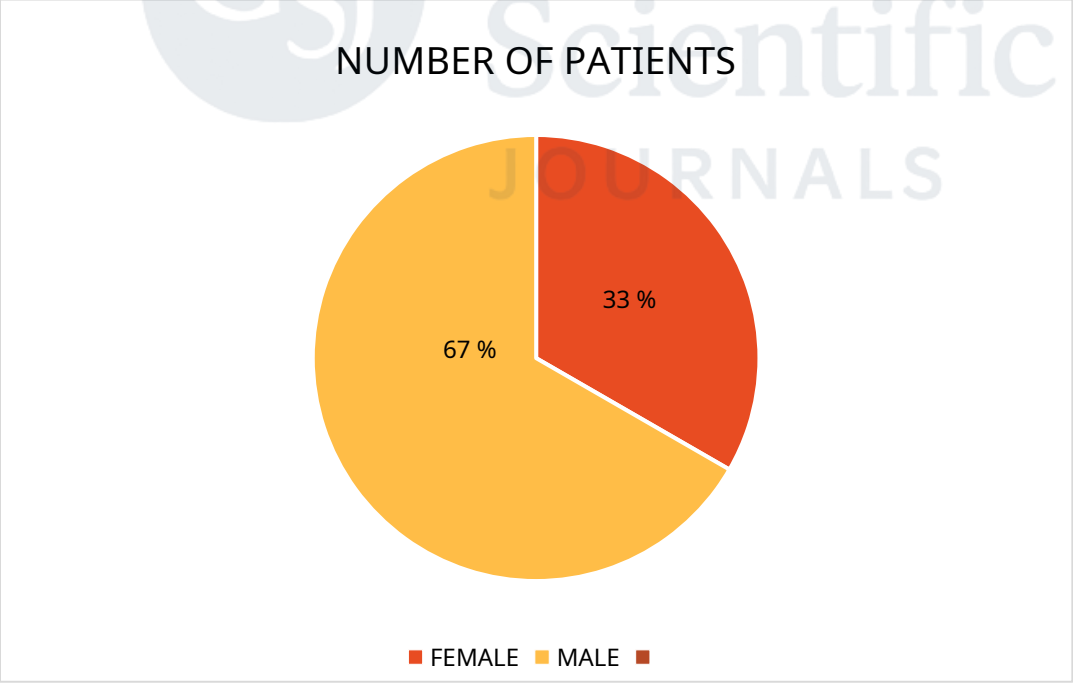


Fig. 4. EFFECT OF MUCORMYCOSIS ON MALE AND FEMALE PATIENTS

Fig.5. Mucormycosis infections around the world: The estimated rates of mucormycosis infection per 100 K individuals around the world is illustrated in this figure. Among the countries, the mucormycosis burden is the highest in countries like India and Pakistan and followed by Portugal. This estimation was compiled by The Leading International Fungal Education (LIFE) portal.

DISCUSSION

The etiologic agent of mucormycosis are ubiquitous in nature and thus may easily be acquired, and its global epidemiology has been studied by several investigators, and may pose a threat during ongoing pandemic as has been observed in India Due to the steep rise in cases of mucormycosis (black fungus infection) amid the second COVID-19 pandemic wave and its association with severe complications and associated higher fatality rate in post COVID-19 patients, this rare disease is now a notifiable disease in India. It is postulated that the use of non-sterile medical supplies might be associated with spore contamination and higher exposure of patients to mucormycosis. In addition, most patients had underlying diabetes mellitus and received steroids. The

presence of diabetes mellitus is a major predisposing factor for mucormycosis as described in a meta-analysis among 600 (70%) of 851 patients with rhino-orbital–cerebral mucormycosis. The presence of diabetes mellitus among patients with COVID-19 was estimated to be 17% in one study and 9% in another study. However, the presence of diabetes mellitus might be higher in other populations and may be more than 50%. One meta-analysis showed that diabetes mellitus was associated with an odds ratio (OR) of 2.40 (95% CI 1.98–2.91) for severe disease, OR of 1.64 (95% CI 2.30–1.08) in a second meta-analysis, and an OR of 2.04, 95% CI 1.67–2.50 in a third meta-analysis [66]. Corticosteroid are currently the only medication that had shown conclusively to be efective in the treatment of COVID-19 in clinical trials therapy. The RECOVERY trial utilized dexamethasone at a dose of 6 mg intravenous or oral once a day for treatment of COVID-19. Systemic steroids could further exaggerate the underlying glycemic control as well as impede the body's immune system. The use of high dose corticosteroid had been used in patients with COVID-19 disease and the use of such medications required assessment. One study showed that adherence to the use of low dose corticosteroid and good glycemic control were important in having no mucormycosis among 1027 ICU patients despite the use of corticosteroids in 89% and that 40% had diabetes mellitus. The presence of these pre-disposing factors in association with high fungal spore burden in certain localities and communities may set the perfect storm for the development of mucormycosis in patients with COVID-19 patients. The outcome was favorable for patients who had surgical debridement in three case series. With the ongoing COVID-19 pandemic and increasing number of critically ill patients infected with SARS-CoV-2, it is important to develop a risk-based approach for patients at risk of mucormycosis based on the epidemiological burden of mucormycosis, prevalence of diabetes mellitus, COVID-19 disease severity and use of immune modulating agents including the combined use of steroids and immunosuppressive agents in patients with cancer and transplants. A suggested approach for aspergillosis in COVID-19 was developed and a similar approach is needed for mucormycosis in SARSCoV-2 infected patients. Whether a mold prophylaxis is required in high-risk patients need further studies. Early diagnosis of cases of mucormycosis, timely treatment with prescribed drugs and surgical operations, checking glycemic levels and judicious use of corticosteroids in patients with COVID-19 along with adopting appropriate hygienic and sanitization measures would aid in limiting the rising cases of this fungal infection. In-depth studies are required to investigate how COVID-19 is triggering mucormycosis infections in patients

and why mainly most cases are being reported from India as compared to other countries amidst second wave of ongoing pandemic.

Conclusion

Mucormycosis is a life-threatening fungal infection characterized by host tissue infarction and necrosis that occurs mostly in immunocompromised patients and is associated with an increasing incidence and mortality despite the availability of therapeutic tools. Determining whether the patient has invasive aspergillosis or mucormycosis could be challenging at the bedside. In this context, new tools of molecular biology have been developed to obtain earlier diagnosis and start optimal medico-surgical treatment. Comparative studies are needed to better optimize induction and consolidation treatment. Treatment may include control of blood glucose levels, treatment of metabolic acidosis, or tapering of immunosuppressive agents. Treatment then consists of antifungal therapy and, if possible, surgical debridement of affected tissue. Prompt initiation of appropriate therapy is critical for patients with PM. In a study of 70 patients, the majority with PM or disseminated disease, a delay in the initiation of amphotericin B–based therapy associated with a twofold increase in mortality. Lipid formulations of amphotericin B are associated with less renal impairment compared with conventional amphotericin B deoxycholate. Most azole antifungal agents have no significant activity against mucormycosis. These agents include fluconazole and voriconazole, which are commonly used as antifungal prophylaxis or for treatment of Candida and Aspergillus infection. Posaconazole is a newer broad-spectrum triazole that has shown. activity against many species of the order Mucorales Surgery is recommended for patients with localized disease and results in improved outcomes compared with in those treated with antifungal therapy alone. Surgery is usually reserved for patients with unifocal disease and can consist of wedge resection, lobectomy, or pneumonectomy. Surgery for bilateral disease is uncommon but has been shown to be effective for source control.

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