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MUCORMYCOSIS: EPIDEMIOLOGY, CLINICAL FEATURES AND ASSOCIATION WITH COVID-19 PANDEMIC

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ABSTRACT

Mucormycosis, a rare but life-threatening fungal disease, is challenging to diagnose and treat. Presently, COVID-19 associated mucormycosis reported high morbidity and mortality, extravagant treatment costs, and a shortage of antifungal drugs. From the global perspective, the surge in mucormycosis cases signifies a higher number of immunosuppressed patients, improved diagnostics, and improper use of antifungal prophylaxis against Mucorales. Further, the growth and infectivity of fungal spores are intensified by acidic blood pH, low oxygen level, and high glucose and iron level in serum resulting in angioinvasion, thrombosis and, tissue necrosis. So, early and precise diagnosis, settling primarily associated risk factors, surgery in localized infection, judicious use of antifungal agents, controlling nosocomial infection, maintaining personal hygiene, and strictly monitoring blood sugar are crucial preventive measures for Mucorales. If not, other opportunistic fungi such as Aspergillus, Candida, or any Zygomycetes may result in an epidemic as COVID-19 mucormycosis.

We searched various scholarly literature using keywords: black fungus, mucormycosis, COVID-19 mucormycosis in PubMed, Scopus and Google Scholar databases, summarized the clinical features of mucormycosis, and highlighted the reason for an abrupt lethal outbreak in COVID-19 patients.

Keywords: Black Fungus, COVID-19, Mucorales, Mucormycosis, Opportunistic infection

INTRODUCTION

Mucormycosis, commonly known as Black Fungus disease, is a rare but deadly fungal infection caused by Mucorales. In the scientific classification, Mucorales are the foremost order of Class-Zygomycetes, Phylum-Zygomycota, and Family-Mucoraceae. Under the class Zygomycetes, three principal orders-Entomophthorales, Mucorales, and Mortierellales cause zygomycotic infections in humans and animals [1], [2]. The systematic classification of clinically important members of Mucoraceae and the other family falling into order "Mucorales" and the Class "Zygomycetes" is illustrated in **Figure1** [2], [3]. From an ecological perspective, the universally occurring Mucorales are most studied saprophytic fungi characterized by coenocytic hyphae that grow at a wider temperature range of 25°C-55°C on organic substrates, reproduce sexually (zygospores) and asexually (sporangiospores), and also live as parasites in plants, animals, and commensals in humans. A recent investigation on Mucorales at the species level in soil samples of different landforms of France reported *Rhizopus arrhizus, Mucor circinelloides, Lichtheimia corymbifera, Rhizopus microsporus,* and *Cunninghamella bertholletiae* to be common and frequent species in the order [3]. The transmission mode is due to fungal spores disseminated by air and inhaled or ingested through contaminated food. Mucorales are challenging to diagnose, and they cause deadly diseases on a larger scale than other opportunistic fungi in pre-existing immunocompromised conditions such as uncontrolled diabetes mellitus, organ transplant, autoimmune disorder, and malignancy. There is an utmost need for early detection of mucormycosis for successful clinical management and improved survival because the clinical feature is non-specific and often becomes too late for effective treatment when it becomes apparent that the patients already have developed mucormycosis [2], [3].

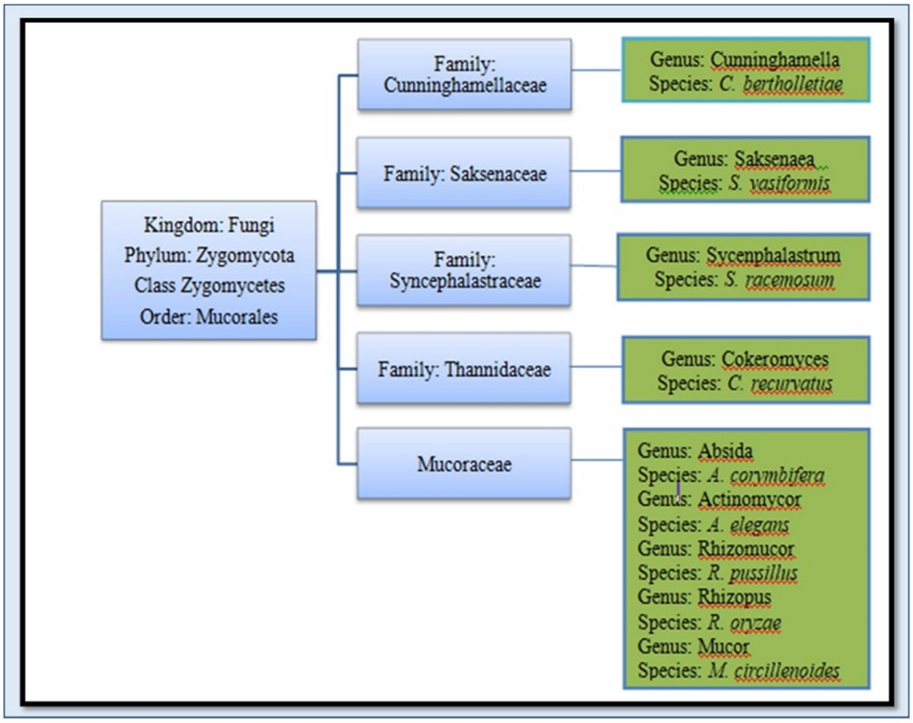

Fig.1 Scientific classification of fingi defining Mucoraceae family

This review article summarizes the clinical features of mucormycosis and its progression to an epidemic in many countries linked to the current COVID- 19 pandemic. Also, it highlights the associated risk factors and preventive measures to control and further safeguard any unforeseen outbreaks by other similar fungi, evident from the recently published peer-reviewed manuscripts on databases like Scopus, PubMed and Google Scholars when searched with keywords: black fungus, mucormycosis and COVID-19 mucormycosis.

EPIDEMIOLOGY

At present, mucormycosis cases are ubiquitous, with differences in incidence and distribution between developing and developed countries. In developing countries, for example, India, the disease is common and mainly affecting diabetic patients, whereas, in developed countries, it is prevalent mainly amongst hematological malignancies [4]. According to a study from Europe, the common clinical manifestations of mucormycosis are rhino-orbito-cerebral (25-39%), pulmonary (24-30%), cutaneous (19-26%) and disseminated (15-23%) types respectively [5].

The global rise in mucormycosis cases is observed due to an increasing number of immunocompromised patients, improved diagnostics, and improper use of antifungal prophylaxis against Mucorales [6]. Ominously, breakthrough

mucormycosis has emerged with the introduction of posaconazole and isavuconazole, irrespective of their effectivity for many Mucorales species [7]. Besides being formerly observed only as a community-acquired fungal infection, it has rapidly turned out to be a nosocomial infection due to various medical interventions, invasive and non-invasive procedures, and equipment used in a hospital setting. Recently in China, Cheng et al. reported an outbreak of hospital-acquired gastrointestinal (GI) mucormycosis caused by Rhizomucor microspores in patients suffering from blood cancer. Upon investigation, it was found that the possible contaminating fungal sources were ready- made food products and cornstarch used in allopurinol oral tablets [8].

The most common form of infection by Mucorales is Rhino-cerebral mucormycosis that frequently occurs in patients with haematological malignancy receiving stem cell transplants [9].

PATHOGENESIS

The major routes of infection are inhalation or ingestion of sporangiospores and traumatic inoculation of conidia resulting in angioinvasion, thrombosis, and tissue necrosis. Nosocomial outbreaks are rare and associated with medical equipment, ventilation systems, and contaminated dressings [10].

In healthy individuals, fungal spores and hyphae are engulfed and neutralized by phagocytic cells such as neutrophils, macrophages, and dendritic cells by the process of receptor-mediated phagocytosis whereby the intracellular killing of the pathogen is carried by oxygen-dependent and oxygen-independent mechanisms. In hyperglycemia and acidosis conditions, zygomycetes resist phagocytosis by impairing chemotaxis and escape phagocytic lysis. In addition, the enzyme called ketone reductase produced by Rhizopus further promotes growth in such conditions. Also, Mucorales display innate resistance to the phagocytosis mechanism contributing to overall pathogenicity [11], [12]. Patients with diabetic ketoacidosis and blood pH below 7.4 have circulatory iron overload due to elevated levels of ferritin protein in serum and this protein normally stores the iron inside cells [13], [14]. Patients with increased serum iron concentration are more vulnerable to angio-invasive mucormycosis that subsequently leads to blood coagulation and finally disseminate into multiple organs such as the heart, kidney, bone and GI tract and causes local tissue destruction [15]. The sequential events in the disease progression are outlined in **Figure 2** [11]–[15].

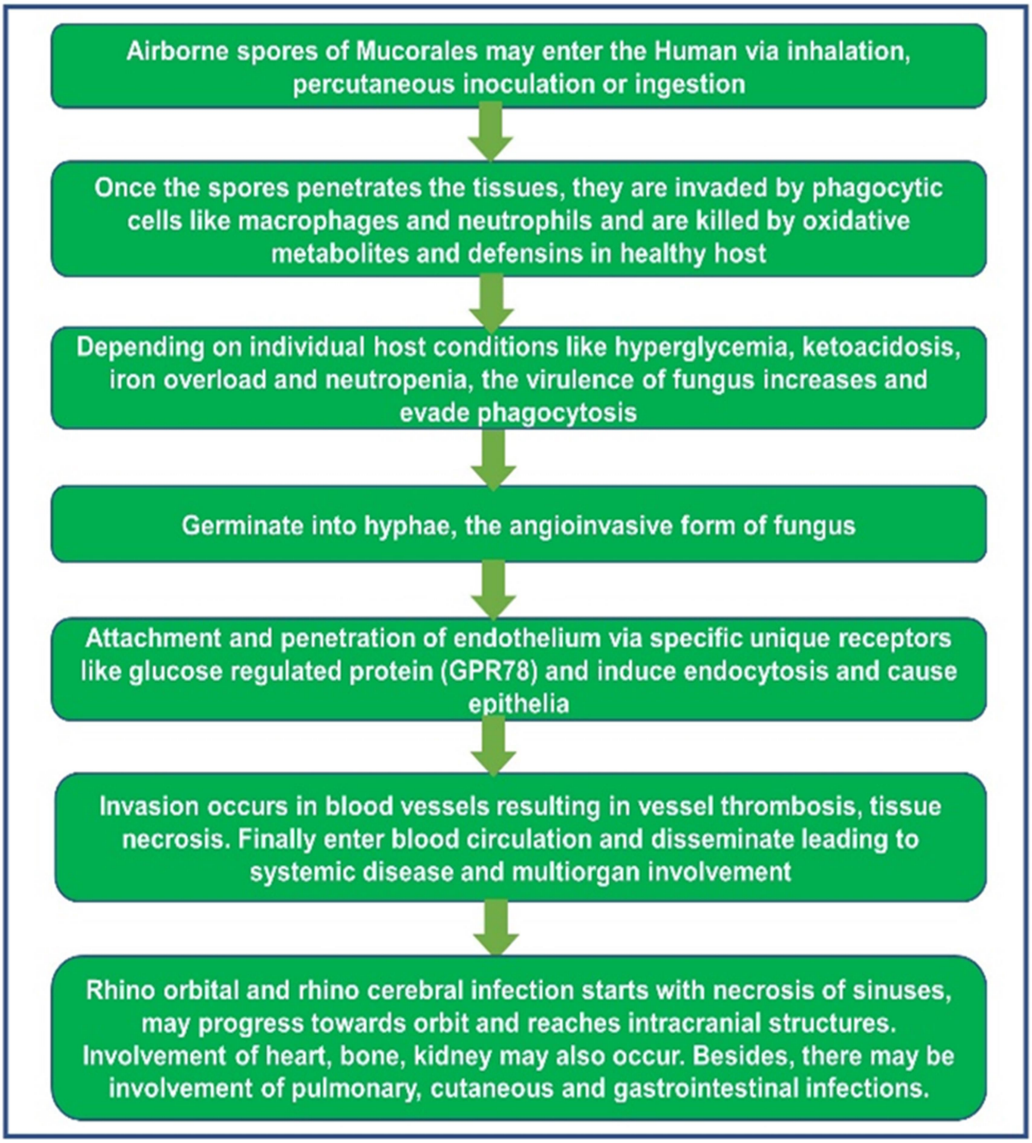

Fig. 2 Pathogenesis of Mucormycosis

RISK FACTORS

A recent review from 2000 to 2017 comprising 851global cases of all mucormycosis types mentioned the following underlying risk factors [16], [17]:

- Diabetes mellitus with or without ketoacidosis
- Malignancies
- Organ/stem cell Transplantations
- Trauma
- Prolonged neutropenia
- Human immunodeficiency virus
- Increased serum ferritin level
- Autoimmune disorders
- Malnutrition
- Long-term corticosteroid use
- Immunosuppressive agents use

- Premature birth and low fetal birthweight
- Injudicious use of antifungals
- Liver disease/renal failure/chronic alcoholism
- Use of non-sterile products in healthcare
- Environmental factors such as air and water

DIAGNOSIS

The primary and convenient methods for diagnosis are direct microscopy, fungal culture, and histotechnology, but these are lesser sensitive and time-consuming [18]. The genetic analysis for examples In-situ-hybridization (ISH) and polymerase chain reaction (PCR) techniques provide reliable and prior detection of the specimen for the earlier start of the treatment [19].

In the tissue specimens, the Grocott-Gomori methenamine silver (GMS) staining technique is preferred over the commonly used Gram stain and lactophenol cotton blue (LCB) stain as GMS outlines the fungal specimen by staining fungal cell wall polysaccharide component. Mucorales have coenocytic (non-septate) hyphae with branching at right angles, while Aspergillus, belonging to the same class, have septate hyphae with branching at acute angles. Despite low sensitivity, direct microscopy techniques are helpful in validating the diagnosis because even if the histopathology analysis demonstrates the characteristic organism, the culture may show no growth, and available serological markers [(1,3)-β-D glucan and Aspergillus galactomannan)] for detecting invasive mucormycosis may also result negative. All microscopy-positive cases may result in only one-third of culture-positive cases due to the homogenization step involved in processing tissue specimens that may destroy fungal hyphae [18], [19].

The clinical diagnostic method involves imaging techniques such as computerized tomography (CT) scan to differentiate invasive fungal infections but the concrete diagnosis requires laboratory methods. Molecular diagnostic approaches such as nucleic acid hybridization techniques, polymerase chain reaction (PCR) based techniques, classical and next-generation DNA sequencing methods and analytical techniques like mass spectrometry for biomarker assay are considered sensitive and confirmatory tests [20], [21].

A summary of different diagnostic methods for the identification of mucormycosis infection is outlined in **Table 1** [18]–[22].

Table 1: Diagnostic methods for mucormycosis

Diagnostic methods	Application	Issues	Efficacy
Wet mount (Direct examination with KOH under fluorescent microscope)	**For a rapid and presumptive diagnosis**	**Lacks colour contrast, specificity and unable to identify at the species level**	**Low**
Histopathology/ cytopathological examination	**For a rapid, economical, and presumptive diagnosis of invasive fungal infection using stain like Periodic Acid Schiff (PAS) which highlights the fungal cell wall in tissue biopsies / bronchoalveolar lavage (BAL)**	**Difficult to distinguish Mucorales from other molds**	**Relatively high**
Culture	**Allows identification at the species level and also useful for testing of antifungal drugs resistance**	**All microscopically confirmed positive cases may show only one-third of positive cases while culturing due to the delicate hyphae**	**Low**
PCR (Polymerase Chain Reaction)	**Amplification of the spore coating protein homolog encoding CotH gene that are universally present among Mucorales**	**Lack of standardization**	**High**
Real time quantitative PCR (qPCR)	**Uses specific probes targeting ribosomal RNA for the identification at species level and for epidemiological surveillance**	**More expensive than conventional PCR and more validation of the test required**	**High**
PCR coupled with electrospray ionization mass spectrometry (PCR/ESI-MS)	**Very effectively identify Mucorales at species level detecting nuclear or mitochondrial genes and efficient than other molecular methods**	**Costly and limited availability**	**High**
Internal Transcribed Spacer (ITS) sequencing	**Most widely sequenced DNA region for understanding relationship at the intra- and interspecies of Mucorales**	**Not broadly used**	**High**
Serology: Lateral Flow Immunoassay (LFIA)	**Uses monoclonal antibodies to detect "Fucomannan" secreted into clinical samples such as BALF, serum, urine and tissue**	**Specific antigen detecting immunoassay for mucormycosis is not available to date similar to other invasive fungal infections like Histoplasmosis and Aspergillosis. Additional investigation required for the validation of the test**	**Relatively higher than ELISA**
Susceptibility testing (Fluorescence-based microplate assay)	**Commonly used for Aspergillus to determine the drug potency against infection**	**Has not been completely evaluated for Zygomycetes**	**Undefined**
Metabolomics-Breath Test	**Non-invasive technique that uses metabolites to detect Mucorales species based on separate breath profiles by individual fungi and also to monitor a response to treatment.**	**Needs further evaluation**	**Undefined**
Imaging Techniques Computed tomography (CT) and 18F-FDG PET-CT Positron emission tomography (PET) radiolabelled with 8F-fluorodeoxyglucose (18F-FDG)	**For differentiating between invasive and non-invasive fungal infections.**	**Confirmatory diagnosis requires histopathology and culture.**	**Low**

TREATMENT

The difficulties in the mucormycosis treatment are due to the rapid dissemination of fungal specimens to multiple sites with general clinical signs and innate resistance against host defense mechanism and antifungal drugs. The effective management of mucormycosis can be done by settling underlying risk factors and surgery, which is the central mode for the control [23], [24]. Clinical management involves multifaceted approaches such as surgically removing

fully or partially infected tissues/organs, appropriate use and doses of antifungal agents, and various concomitant treatment proceedings [25], [26]. Pertaining to safety, efficacy and long-term use of the drug, the standard and primary choice of antifungals are lipid formulations of Amphotericin B (L-AMB). The broad spectrum triazoles Posaconazole and Isavuconazole are used as salvage therapy to patients not responding to Amphotericin B. As the oral formulation of Amphotericin B is not available, these triazoles are useful for outpatient treatment therapy as well as oral step-down therapy to patients responding to Amphotericin B. Given the rarity of the disease, randomized control trials are not practically possible, lacking the valid evidence to establish the 'gold standard' method for efficient treatment [27]–[30].

Future treatment is targeted to the immunomodulatory response of the host, targeted immunotherapy, and metabolomics [31]. Surgery, when needed, is performed quickly and aggressively, to excise not only dead tissues but also fungal infected surrounding healthy alike tissues [20], [25]. Surgery is limited to localized infection and mainly helpful in rhino-orbital cerebral infection and necrotizing soft tissue and not possible in disseminated infection and the remoteness of the infected organ [20], [25], [26]. Susceptibility testing of fungi is suggested by the regulatory bodies to gain empirical evidence for establishing therapeutic strategy and epidemiological knowledge [27], [28].

Mucormycosis (MCR) in COVID-19

COVID-19 is the ongoing worldwide pandemic caused by a highly infectious novel coronavirus first identified as SARS-CoV-2 in China in December 2019. The pathophysiology of the virus is still under study because of the evolving mutant variants of the virus globally. With this, the additional and new clinical presentations and complications of the disease are being recognized [32].

The classic symptoms of COVID-19 disease may vary from very mild or even asymptomatic to life-threatening pneumonia [33], [34]. COVID-19 patients were also reported with severe opportunistic bacterial and fungal infections such as Staphylococcal infection, gram-negative bacterial infection, oropharyngeal candidiasis, and pulmonary aspergillosis [35]. Such infections were particularly common to patients having comorbidities with diabetes mellitus (DM) and Chronic obstructive pulmonary disease (COPD) [36][37]. Other predisposing factors contributing to co-infections were the patient's treatment in intubation, broad-spectrum antibiotics, treatment with monoclonal antibodies and corticosteroids.

The corticosteroids are commonly used to treat seriously ill COVID-19 patients to minimize the hypersensitivity and inflammatory reactions exhibited by the host defense mechanism against the virus. However, the corticosteroids used are immunosuppressive and increase insulin resistance, eventually elevating blood glucose levels in any individual leading to a diabetic condition. The combined immunocompromised and diabetic conditions lead to fungal infection by Mucorales [38]–[40].

Studies reveal that SARS CoV-2 causes damage to insulin-producing pancreatic β cells resulting in type -1 diabetes mellitus with ketoacidosis [41], [42]. The plausible reason for this "diabetogenic state" can be due to the overproduction of angiotensin-converting enzyme 2 (ACE2) receptors, high serum ferritin level, and cytokine storm. ACE2 acts as a SARS-CoV-2 receptor present in vascular endothelial cells, lungs, heart, kidneys, liver, intestine, microglial cells, and adipose tissue where damage and inflammation can result in tissue necrosis, deep vein thrombosis, pulmonary embolism, cardiac and renal dysfunction, gut dysbiosis, meningitis and encephalitis, and even psychological problems [14], [15], [41], [42].

In addition, severe COVID-19 results in hyperferritinemic syndromes in which the generated reactive superoxides (O_2^-) causes fibrosis through the redox damage, and this process is further escalated by cytokine storm, especially IL-6, which eventually leads to multi-organ failure. Also, high serum ferritin level leads to circulatory iron overload that makes blood pH acidic, conferring one of the susceptibility factors to develop mucormycosis (MCR) [11], [18]. Pulmonary vascular endothelialitis further contribute to mucormycosis in COVID-19, which was evident from the postmortem examination of COVID-19 patients and was found more severe than casualty due to influenza A (H1N1) [12], [15]. Both, acidemic states and high blood glucose levels facilitate Mucorales spore coat protein homologs (CotH) to adhere and penetrate endothelium via glucose-regulated protein (GRP-78) receptor [4], [41].

Patients with uncontrolled Diabetes Mellitus are in immunocompromised states. The germination and invasion of fungal spores are intensified by acidic blood pH, reduced oxygen level and high serum levels of glucose, ketone bodies, and iron [43]. The vegetative forms invade vessels to form a thrombus that ultimately leads to the necrosis of adjacent tissues [10]. Covid

Associated Mucormycosis (CAM) has been related to high morbidity and mortality, extravagant treatment costs, and a shortage of antifungal drugs. Immunocompromised individuals such as patients with uncontrolled diabetes, organ transplant patients, cancer patients, HIV-positive patients, and any person taking immunosuppressive drugs including steroids are at higher risk. The black lesions on any part of the body are an indicator of this disease progression [44], [45].

PREVENTION

Some of the evidence-based preventive measures that can be taken for the control and management of COVID-19 mucormycosis are [6], [27] :

1. Environmental sanitation to prevent exposure to decaying organic matters like bread / fruits / vegetables / soil / compost / feces.
2. Regular testing of serum glucose level in diabetes, COVID-19 patients, COVID-19 discharged patients, and one undergoing treatment on steroids.
3. Monitoring blood glucose level in COVID-19 patients that require treatment with steroid.
4. Judicious use of steroid – correct timing, correct dose and duration.
5. Judicious use of antibiotics and antifungals
6. Use of clean and sterile water for humidifiers during oxygen therapy
7. Immunocompromised and receiving corticosteroids should rule out the exact cause of the nasal blockage, if got any
8. Get informed about the initial clinical features of mucormycosis and seek for immediate treatment.
9. Basic examinations like pupillary reaction, ocular motility, sinus tenderness and palatal assessment should be a part of regular physical assessment of a COVID-19 patient.

CONCLUSION

Mucormycosis is a rare and deadly disease caused by a fungal commensal of human nasal mucosa of the Zygomycetes class and acts as an opportunistic pathogen in an immunocompromised individual with conditions such as diabetes, ketoacidosis, organ transplantation, HIV infection, cancer, severe burns.

Early detection of mucormycosis by employing molecular biology techniques, such as in-situ-hybridization (ISH) and polymerase chain reaction (PCR), is crucial for successful clinical management and improved survival [20], [21]. Mucorales disseminates rapidly to multiple body sites with general clinical signs and exhibit intrinsic resistance against host defense mechanism and antifungal drugs. So, the

clinical management involves settling underlying risk factors, surgery, and appropriate use and doses of antifungal agents. The first choice of drug antifungals are lipid formulations of Amphotericin B (L-AMB), and broad-spectrum triazoles, Posaconazole and Isavuconazole are used as salvage and step-down therapy [23], [24], [26]. Future treatments are targeted to the immunomodulatory response of the host, targeted immunotherapy, and metabolomics [31].

Lately, this disease is associated with COVID-19 that also predisposes to the immunosuppressed state aiding rapid dissemination of the infection increasing both morbidity and mortality [43], [44]. In addition, patient's treatment in mechanical ventilation, antibiotic therapy, use of immunomodulators, steroids, and supplements such as zinc, iron, and associated high blood sugar level provoke fatal effects. The judicious use of antibiotics, antifungals, steroids, proper sterilization of medical instruments and equipment used for diagnosis and treatment, personal hygiene, strict blood sugar control, and monitoring in both diabetic and non-diabetic patients are crucial preventive measures for the mucormycosis epidemic in the current COVID -19 pandemic [38], [39], [45].

If proper corrective measures, diagnosis, treatment, and management of fungal infections are not established then other fungi such as Aspergillus, Candida, or any Zygomycetes can emerge into a deadly opportunistic pathogen in an immune suppression state and may result in an epidemic just like COVID-19 mucormycosis.

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