



Mini Review

## Post-COVID Mucormycosis: An Emerging Threat in Developing Countries - A Prospective Review

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### Abstract

COVID-19, with its rapidly mutating strains, poses a significant global health challenge. Recent reports of a surge in mucormycosis cases among COVID-19 patients highlight the urgent need for understanding and addressing this critical complication. This review explores the factors contributing to mucormycosis development in COVID-19 patients and outlines strategies for prevention and management. Several factors, including high glucose levels (diabetes, onset, steroid-induced hyperglycemia), low oxygen levels, elevated iron levels (especially ferritin), metabolic acidosis, and diabetic ketoacidosis, can facilitate the germination of mucor spores. COVID-19 patients with underlying conditions such as diabetes, cancer, or organ transplants are particularly susceptible to mucormycosis due to their immunocompromised state. The growth of the mucor pathogen requires free iron, which is elevated in conditions like diabetic ketoacidosis. This elevated iron level promotes the formation of Cot-H, a crucial component of fungal growth, leading to mucormycosis. Additionally, comorbidities and corticosteroids can suppress the immune system, hindering the body's ability to fight off infections like mucormycosis. Therefore, it is imperative to avoid the indiscriminate use of corticosteroids. Strict control of acute hyperglycemia and comprehensive monitoring of diabetic and immunocompromised COVID-19 patients are essential preventive measures. By addressing these factors, healthcare providers can mitigate the risk of mucormycosis in COVID-19 patients and improve overall outcomes.

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## INTRODUCTION

The term "corona" is derived from the Greek word for "crown," aptly describing the appearance of the virus under a microscope: a spherical particle adorned with a crown-like structure of protein spikes, known as peplomers<sup>1</sup>. These peplomers enable the virus to attach to and infect host cells. Throughout history, humanity has faced numerous pandemics, including the Bubonic Plague (1665), the Spanish Flu (1918-1919), the Asian Flu (1957), the Hong Kong Flu (1968), the Swine Flu (2009), and, more recently, the COVID-19 pandemic, declared by the WHO on February 11, 2020<sup>2</sup>. The novel coronavirus responsible for COVID-19 was first identified in Wuhan, Hubei Province, China, in late 2019<sup>3</sup>.

Mucormycosis, a rare but potentially fatal fungal infection, was first described by Paltauf in 1885 as phycomycosis<sup>4</sup> and later as mucormycosis by Baker in 1957<sup>5</sup>. This opportunistic infection is caused by a group of fungi, primarily from the order Mucorales, commonly found in the environment, including soil, decaying organic matter, and even the human microbiome<sup>6</sup>. In recent years, there has been a surge in mucormycosis cases, particularly among individuals recovering from COVID-19<sup>7,8</sup>. This mini review aims to explore the factors contributing to the increased incidence of mucormycosis in COVID-19 patients and to discuss preventive measures to mitigate this risk.

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## PREVALENCE OF COVID-19

The COVID-19 pandemic has led to a global health crisis, with millions of deaths reported to the WHO<sup>9</sup>. However, the actual number of deaths may be significantly higher, particularly in countries like India, where the pandemic has been exacerbated by the emergence of mucormycosis. While the global prevalence of mucormycosis is relatively low, India has experienced a dramatic surge in cases, with a prevalence rate 80 times higher than developed countries<sup>10,11</sup>.

Diabetes mellitus is the most common risk factor for mucormycosis in India, whereas cancer and organ transplantation are leading risk factors in Europe and the United States<sup>12</sup>. However, diabetes remains a significant risk factor globally, contributing to a high mortality rate of 46%<sup>13</sup>. Several factors, including high glucose levels, low oxygen levels, high iron levels, metabolic acidosis, and immunosuppression due to steroid use or underlying conditions like cancer or HIV/AIDS, can predispose individuals to mucormycosis<sup>14</sup>. The most common site of infection is the rhino-maxillary region, particularly in immunocompromised individuals with diabetes or those receiving steroid therapy<sup>15</sup>.

## MUCORMYCOSIS CASES OF COVID-19 PATIENTS

Recent studies have highlighted a concerning association between COVID-19 infection, uncontrolled diabetes mellitus, and subsequent mucormycosis. For instance, a case report involving a 60-year-old diabetic patient who tested positive for COVID-19 and received treatment with methylprednisolone, oseltamivir, and meropenem eventually developed mucormycosis, as confirmed by nasal biopsy. Similarly, a larger study involving 18 patients with poorly controlled diabetes and a history of steroid use found that 17 (94%) were diagnosed with mucormycosis<sup>16-18</sup>. These findings underscore the importance of vigilant monitoring for mucormycosis in high-risk individuals, particularly those with diabetes and COVID-19 (Table I).

Several case reports and studies have highlighted the association between COVID-19 infection and mucormycosis. For instance, a 40-year-old woman and a 54-year-old man with severe COVID-19 infection and corticosteroid treatment developed mucormycosis, confirmed by nasal endoscopy and radiological findings<sup>19</sup>. Similarly, a study involving 25 patients with invasive mucormycosis revealed that 11 of them had concurrent COVID-19 infection, suggesting a potential link between the two diseases, particularly in immunocompromised individuals<sup>20</sup>. A middle-aged diabetic woman with COVID-19 and facial pain, ptosis, and fever was diagnosed with mucormycosis through sinus endoscopy and histopathological examination<sup>21</sup>. A comprehensive review of 101 reported cases of mucormycosis in COVID-19 patients identified diabetes and corticosteroid use as significant risk factors<sup>14</sup>.

**Table I.** Mucormycosis Cases of COVID-19 Patients.

No.	Description	Diabetes	Use of Corticosteroids	COVID-19 Positive	Mucormycosis	Treatment for Mucormycosis	References
1	60-year-old patient	Yes	Yes	Yes	Yes	Amphotericin B	16
2	Study of 18 COVID-19 positive patients	Yes	Yes	Yes	17/18 patients	-	18
3	40-year-old female and 54-year-old male patients	No	Yes	Yes	Yes	Amphotericin B	19
4	Study of 25 patients	No	Yes	11/25 patients	All 25 patients	-	20
5	Middle-aged woman	Yes	Yes	Yes	Yes	Amphotericin B	21
6	Study of 101 patients with COVID-19 and mucormycosis	80/101 patients	77/101 patients	Yes	Yes	Amphotericin B	14
7	3 patients (2 male, 1 female)	Yes	No	No	Yes	Surgery	22
8	Study of 2 male patients aged 60 and 67 years	Yes	No	No	Yes	Amphotericin B	23

## CURRENT SITUATION OF MUCORMYCOSIS AND COVID-19

The rapid and ongoing spread of COVID-19, coupled with its high mutation rate, has presented a significant global health challenge. The virus's ability to evolve quickly has hindered efforts to control its transmission and develop effective countermeasures. The SARS-CoV-2 virus has undergone various mutations, leading to the emergence of several variants of concern. Notably, the B.1.617.1 (kappa) and B.1.617.2 (delta) variants were first identified in India<sup>24</sup>. Other significant variants include B.1.1.7 (alpha) from the UK, B.1.35.1 (beta) from Africa, P.1 (gamma) from Brazil, B.1.427/B.1.429 (epsilon) from the USA, P.2 (zeta) from Brazil, and B.1.525 (eta) from multiple countries<sup>25</sup>. Given the rapid emergence of COVID-19, the development of a specific drug within a short timeframe has proven challenging. As such, non-pharmaceutical interventions like lockdowns and vaccination have been the primary strategies for preventing the spread of the virus and mitigating its impact. While vaccines cannot directly eliminate the virus, they effectively stimulate the immune system to generate a robust response, providing protection against infection and severe disease<sup>26</sup>.

Several vaccines, including BNT162b2/Comirnaty Tozinameran (Pfizer), AZD1222 (AstraZeneca), Covishield (Serum Institute of India), Ad26.Cov2.5 (Janssen), mRNA-1273 (Moderna), SARS-CoV-2 (Vero cell) (Sinopharm/BIBP), and Sputnik V (Gamaleya National Centre), have received regulatory approval, while numerous others are under review or in clinical trials<sup>27</sup>. While vaccination remains a primary strategy to combat COVID-19, antibody-based therapies have emerged as a promising complementary approach. Monoclonal antibodies targeting the SARS-CoV-2 spike protein can neutralize the virus and prevent infection. However, the emergence of viral variants with mutations in the spike protein can reduce the effectiveness of these therapies. To address this challenge, researchers are exploring the development of antibody cocktails that target multiple epitopes on the viral surface, thereby reducing the likelihood of viral escape. This strategy has shown promise in preclinical and clinical studies and is now gaining increasing attention from scientists and clinicians<sup>28,29</sup>.

The global health crisis caused by COVID-19 has been further exacerbated by the emergence of secondary infections, such as mucormycosis<sup>30</sup>. In countries like India, a significant number of COVID-19 patients have experienced severe complications due to mucormycosis<sup>6</sup>. This opportunistic fungal infection primarily affects individuals with underlying health conditions, including diabetes, metabolic acidosis, and diabetic ketoacidosis. Patients with elevated blood glucose levels, low oxygen saturation, and high iron levels are particularly susceptible to mucormycosis<sup>31,32</sup>.

Iron is an essential element for both mammalian cells and pathogens<sup>33</sup>. In the mammalian host, iron is tightly bound to carrier proteins such as transferrin, ferritin, and lactoferrin to prevent its toxic effects. However, pathogens, including fungi, require free iron for their growth and proliferation. Diabetic ketoacidosis (DKA) can disrupt iron homeostasis by lowering the iron-binding capacity of carrier proteins, leading to increased levels of free iron in the serum. This elevated free iron concentration can provide a favorable environment for fungal growth and infection<sup>34-36</sup>.

A compromised immune system, often resulting from long-term steroid use, cancer, organ transplantation, or other underlying health conditions, can increase susceptibility to mucormycosis<sup>37</sup>. While the precise pathophysiology of mucormycosis remains unclear, a proposed mechanism linking COVID-19 to mucormycosis is illustrated in **Figure 1**. The overwhelming demand for oxygen during the COVID-19 pandemic, particularly in India, led to a shortage of medical-grade oxygen cylinders. Consequently, hospitals were forced to use industrial-grade cylinders, which may have been inadequately cleaned and sterilized. This potential contamination with fungal spores could have contributed to the increased incidence of mucormycosis among COVID-19 patients<sup>38</sup>.

While the definitive treatment for this condition remains unclear, current literature suggests that amphotericin B and surgical intervention may be potential therapeutic options<sup>39-41</sup>. Additionally, certain homeopathic remedies, such as arsenic album, marksol, gelsenium, nux vomica, sulphur, tuberculinum, and pulsatilla, have been reported to offer potential therapeutic benefits<sup>42,43</sup>. However, further rigorous scientific studies are needed to validate the efficacy and safety of these treatments.

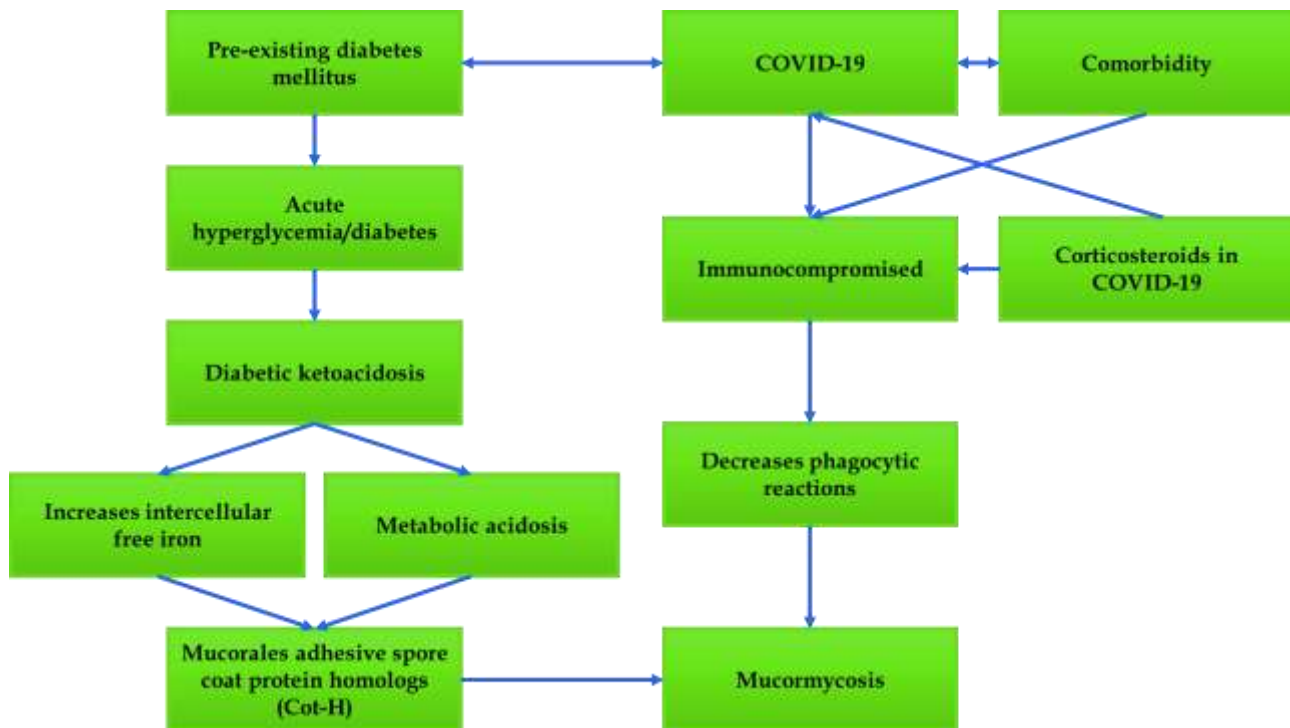


Figure 1. Pathogenesis of mucormycosis in COVID-19 patients.

## CONCLUSION

the global COVID-19 pandemic has underscored the importance of comprehensive infection control measures and timely treatment of opportunistic infections like mucormycosis. To mitigate the risk of mucormycosis, it is crucial to minimize the use of corticosteroids, especially in immunocompromised individuals, and to strictly control blood glucose levels in diabetic patients. Early diagnosis and prompt initiation of appropriate antifungal therapy, such as liposomal amphotericin B, posaconazole, or isavuconazole, are essential for improving patient outcomes. Additionally, surgical intervention may be necessary to debride necrotic tissue. Ongoing research is needed to develop novel antifungal agents with improved efficacy and safety profiles, as well as to explore preventive strategies to reduce the incidence of mucormycosis in high-risk populations.

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## AUTHORS' CONTRIBUTION

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**Funding acquisition:** -

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## DATA AVAILABILITY

None.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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