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REVIEW ARTICLE

Opportunistic mucormycosis infection in patients with COVID-19

Infección oportunista por mucormicosis en pacientes con COVID-19

Infecção oportunista por mucormicose em pacientes com COVID-19

Marcela Alejandra Altamirano-Salazar[1], Alejandro Patricio Jaramillo-Aguilar[1], Francisco Xavier Poveda-Paredes[1]

[1]Universidad Regional Autónoma de Los Andes, Ambato. Ecuador.

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ABSTRACT

Introduction: COVID-19 pandemic has generated infectious complications with significant clinical impact, among them mucormycosis, an invasive mycosis that primarily affects immunocompromised patients and those with uncontrolled diabetes mellitus.
Objective: to analyze the relationship between mucormycosis and COVID-19, identifying risk factors, clinical manifestations, and treatments.
Methods: a literature review was conducted, identifying sources from different databases through a search algorithm. The selection and analysis of those that met the inclusion and exclusion criteria allowed the topic to be addressed through a critical and structured analysis, ensuring methodological rigor and transparency throughout the process.
Development: a significant increase in COVID-19-associated mucormycosis has been evidenced, especially in countries with a high prevalence of diabetes. The main predisposing factors were corticosteroid-induced hyperglycemia, diabetic ketoacidosis, and states of immunosuppression. The most frequent clinical presentation was the rhino-orbital-cerebral form, although pulmonary, cutaneous, and gastrointestinal cases were also documented. Early diagnosis through microbiological tests and imaging is crucial to improve prognosis. The recommended treatment combines systemic antifungals, mainly liposomal amphotericin B, with surgical debridement in advanced cases. Mortality remains high, underscoring the need for preventive strategies and an interdisciplinary approach.
Conclusions: mucormycosis constitutes a serious complication in patients with COVID-19, favored by the interaction between viral infection, diabetes, and corticosteroid use. It is necessary to strengthen preventive measures, optimize diagnosis, and apply combined therapies to reduce the high associated mortality.

Keywords: COVID-19; Opportunistic Infections; Mucormycosis.

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RESUMEN

Introducción: la pandemia de COVID-19 ha generado complicaciones infecciosas de gran impacto clínico, entre ellas la mucormicosis, una micosis invasiva que afecta principalmente a pacientes inmunocomprometidos y con diabetes mellitus descontrolada.
Objetivo: analizar la relación entre mucormicosis y COVID-19, identificando factores de riesgo, manifestaciones clínicas y tratamientos.
Métodos: se realizó una revisión de la literatura, identificándose fuentes de diferentes bases de datos a partir de un algoritmo de búsqueda. La selección y análisis de aquellas que cumplieron los criterios de inclusión y exclusión, permitió abordar el tema desarrollando un análisis crítico y estructurado, garantizándose en todo momento el rigor metodológico y transparencia del proceso.
Desarrollo: se ha evidenciado un incremento significativo de mucormicosis asociada a COVID-19, especialmente en países con alta prevalencia de diabetes. Los principales factores predisponentes fueron hiperglucemia inducida por corticosteroides, cetoacidosis diabética y estados de inmunosupresión. La presentación clínica más frecuente fue la forma rino-orbito-cerebral, aunque también se documentaron casos pulmonares, cutáneos y gastrointestinales. El diagnóstico temprano mediante pruebas microbiológicas e imágenes es determinante para mejorar el pronóstico. El tratamiento recomendado combina antifúngicos sistémicos, principalmente anfotericina B liposomal, con desbridamiento quirúrgico en casos avanzados. La mortalidad continúa siendo elevada, lo que subraya la necesidad de estrategias preventivas y un abordaje interdisciplinario.
Conclusiones: la mucormicosis constituye una complicación grave en pacientes con COVID-19, favorecida por la interacción entre infección viral, diabetes y uso de corticosteroides. Es necesario fortalecer las medidas de prevención, optimizar el diagnóstico y aplicar terapias combinadas para reducir la elevada mortalidad asociada.

Palabras clave: COVID-19; Infecciones Oportunistas; Mucormicosis.

RESUMO

Introdução: a pandemia de COVID-19 gerou complicações infecciosas de grande impacto clínico, entre elas a mucormicose, uma micose invasiva que afeta principalmente pacientes imunocomprometidos e com diabetes mellitus descontrolada.
Objetivo: analisar a relação entre mucormicose e COVID-19, identificando fatores de risco, manifestações clínicas e tratamentos.
Métodos: foi realizada uma revisão da literatura, identificando-se fontes de diferentes bases de dados a partir de um algoritmo de busca. A seleção e análise daquelas que cumpriram os critérios de inclusão e exclusão permitiram abordar o tema desenvolvendo uma análise crítica e estruturada, garantindo em todo momento o rigor metodológico e a transparência do processo.
Desenvolvimento: evidenciou-se um aumento significativo da mucormicose associada à COVID-19, especialmente em países com alta prevalência de diabetes. Os principais fatores predisponentes foram hiperglicemia induzida por corticosteroides, cetoacidose diabética e estados de imunossupressão. A apresentação clínica mais frequente foi a forma rino-órbito-cerebral, embora também tenham sido documentados casos pulmonares, cutâneos e gastrointestinais. O diagnóstico precoce por meio de exames microbiológicos e de imagem é determinante para melhorar o prognóstico. O tratamento recomendado combina antifúngicos

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sistêmicos, principalmente anfotericina B lipossomal, com desbridamento cirúrgico em casos avançados. A mortalidade continua elevada, o que ressalta a necessidade de estratégias preventivas e de uma abordagem interdisciplinar.
Conclusões: a mucormicose constitui uma complicação grave em pacientes com COVID-19, favorecida pela interação entre infecção viral, diabetes e uso de corticosteroides. É necessário fortalecer as medidas de prevenção, otimizar o diagnóstico e aplicar terapias combinadas para reduzir a elevada mortalidade associada.

Palavras-chave: COVID-19; Infecções Oportunistas; Mucormicose.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, has triggered a series of medical challenges beyond the characteristic respiratory symptoms of the viral infection. Among the emerging complications, mucormycosis, colloquially known as black fungus, has become a significant clinical concern, particularly in patients with severe forms of COVID-19. Mucormycosis, a rare but potentially lethal invasive fungal infection, is associated with various comorbidities, especially uncontrolled diabetes and the use of immunosuppressive treatments.[1]

COVID-19, a term that first appeared in 2019 with the initial cases identified in Wuhan, China, soon became a global pandemic. Mandatory quarantine measures were implemented worldwide due to the high rate of infection and mortality associated with the SARS-CoV-2 virus. This positive-sense single-stranded RNA virus, belonging to the Coronaviridae family, has been responsible for a range of illnesses, from flu-like symptoms to more severe conditions such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[2]

The severity of COVID-19 infection lies in its easy transmission, either through direct contact with infected individuals or indirectly through contact with contaminated surfaces. However, in some COVID-19 patients, the potential presence of other opportunistic pathogens in the environment, such as mucormycosis, has been overlooked. The term mucormycosis encompasses various severe opportunistic infections caused by fungi of the order Mucorales. Although these infections have been known for a long time, the increase in cases in recent decades has renewed interest in them. Currently, mucormycosis represents the third leading cause of invasive fungal infection, primarily affecting patients with poorly controlled diabetes and those who are severely immunocompromised, such as solid organ transplant recipients or patients with hematological malignancies.[3]

Mucormycosis is mainly caused by the inhalation of spores, affecting various parts of the body, with pulmonary and cerebral infections being the most common. The hyperglycemia generated by diabetes provides a favorable environment for the development of mucormycosis, with COVID-19 patients being particularly vulnerable due to corticosteroid treatment and subsequent hyperglycemia.[4] In relation to the aforementioned, the present study has been developed with the objective of analyzing the relationship between mucormycosis and COVID-19, identifying risk factors, clinical manifestations, and treatments.

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METHODS

This study was designed as a systematic bibliographic review conducted in accordance with the PRISMA 2020 guidelines. The objective was to synthesize the available evidence on opportunistic mucormycosis infection in patients with COVID-19. The search period was defined between January 2010 and December 2024, thereby encompassing both pre-pandemic and pandemic years to capture the evolution of scientific knowledge on this topic. The review adhered to a structured protocol that ensured transparency, reproducibility, and methodological rigor.

The information sources included major international databases such as PubMed, Scielo, ScienceDirect, Google Scholar, Lilacs, and BVSALUD. In addition, references cited in the retrieved articles were screened to identify potentially relevant secondary sources. Literature classified as "grey" (conference proceedings, theses, and institutional reports) was also considered when it provided pertinent data on mucormycosis associated with COVID-19. This comprehensive approach was intended to minimize publication bias and ensure the inclusion of diverse forms of evidence.

The search strategy was constructed using a combination of controlled vocabulary and free-text terms. Boolean operators "AND" and "OR" were applied to link descriptors such as "mucormycosis," "COVID-19," "SARS-CoV-2," "risk factors," "treatment," and "opportunistic infection." The search was restricted to articles published in English, Spanish, and Portuguese, reflecting the linguistic scope of the databases consulted. Inclusion criteria comprised studies published within the defined time frame, addressing directly the relationship between mucormycosis and COVID-19, and providing full-text access. Exclusion criteria included duplicate records, articles outside the temporal range, studies without peer review, animal or preclinical studies, and publications lacking sufficient methodological detail.

The selection process was carried out in sequential stages. First, titles and abstracts were screened to exclude irrelevant studies. Subsequently, full-text articles were assessed for eligibility based on the predefined criteria. The initial search yielded a total of 1,224 records. After removing duplicates, 1,067 articles remained. Title and abstract screening excluded 647 records, leaving 420 for full-text review. Of these, 275 were excluded for not meeting eligibility requirements, resulting in 145 articles assessed in detail. Ultimately, 27 studies were included in the final synthesis. The entire process was documented using a PRISMA flow diagram to illustrate identification, screening, eligibility, and inclusion stages (Fig. 1).

Data extraction was performed using a standardized form that captured key variables: author, year of publication, study design, sample characteristics, risk factors, clinical presentation, interventions, and main outcomes. The methodological quality of the included studies was appraised using appropriate tools for each design. The analysis was primarily qualitative, emphasizing thematic synthesis of risk factors, clinical manifestations, and treatment strategies. When sufficient homogeneity was present, quantitative synthesis through meta-analysis was considered. This methodological framework ensured that the review provided a comprehensive and balanced overview of the relationship between mucormycosis and COVID-19, highlighting both strengths and limitations of the available evidence.

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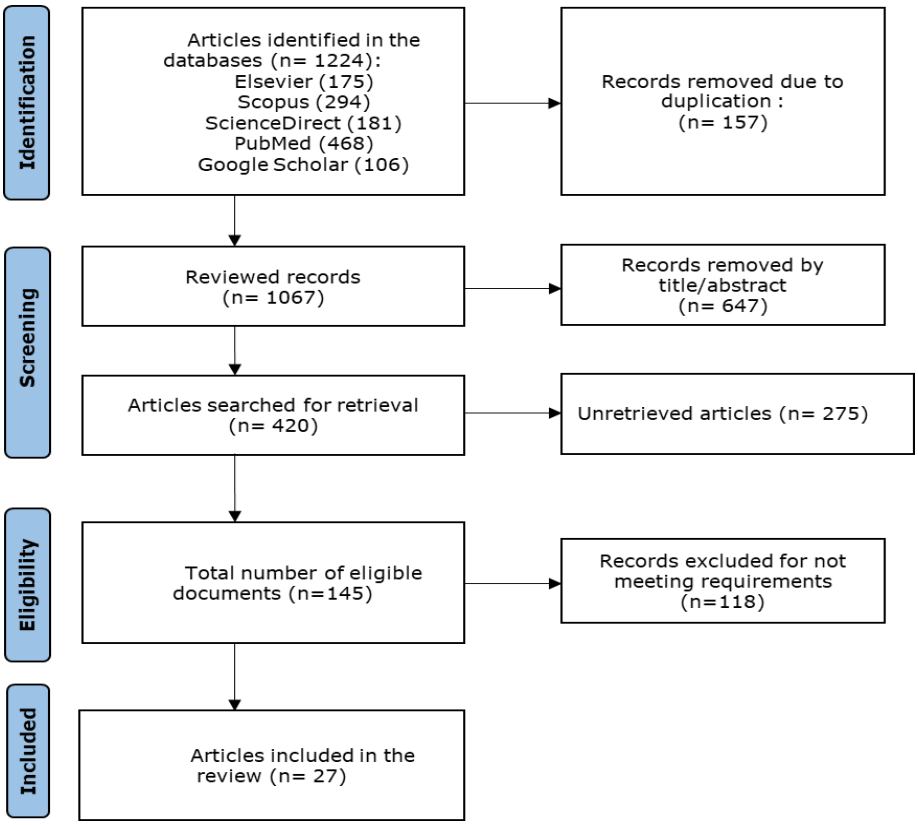

Fig. 1 Flow diagram for article selection.

DEVELOPMENT

The opportunistic infectious disease mucormycosis is caused by fungi belonging to the subphyla Mucormycotina and Entomophthorales. The primary human pathogens of the class Mucormycetes are found in the orders Mucorales and Entomophthorales. Within the Mucorales order, pathogenic genera include Rhizopus, Mucor, Lichtheimia, Rhizomucor, Saksenaea, Cunninghamella, Syncephalastrum, and Apophysomyces. Infections caused by these pathogens are typically acute and progress rapidly, with mortality rates ranging from 70 % to 100 %.[2,4]

Macroscopically, fungi in the Mucorales order grow rapidly and produce woolly colonies that are gray to brown in color, with characteristics that help distinguish them from other pathogens. Microscopic examination reveals filamentous fungi with wide, hyaline, coenocytic hyphae. These fungi reproduce sexually via zygospores and are morphologically characterized by hyaline, wide, and sparsely septate hyphae.[5]

Regarding epidemiology, mucormycosis is globally distributed as these microorganisms are ubiquitous in soil and decomposing vegetation. They spread via inhalation, ingestion, or contamination of wounds with spores, and can also be found in air conditioning systems, including during construction processes. Clinical presentation varies from sinus infections, which are the most common and can be isolated sinusitis, rhinocerebral, or sinoorbital mucormycosis, to gastrointestinal, cutaneous, pulmonary infections, and even dissemination.[6]

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Given that this type of infection affects patients with varying degrees of immunosuppression, it is characterized by rapid progression with high morbidity and mortality. Rhinocerebral mucormycosis begins as an acute invasive infection of the nasal cavity, paranasal sinuses, and orbit, affecting facial structures and extending to the central nervous system, including the meninges and brain. It occurs in patients with metabolic acidosis, diabetic ketoacidosis, or hematological malignancies. On the other hand, pulmonary mucormycosis is a primary infection in neutropenic patients. Pulmonary lesions may appear as infarcts due to hyphal invasion, progressing to thrombosis of large pulmonary vessels. X-rays show rapidly progressing bronchopneumonia, signs of cavitation, and possible fungal masses. It can progress to pulmonary hemorrhage with fatal hemoptysis.[2,6]

Cutaneous mucormycosis indicates hematogenous dissemination of the pathogen, presenting as an erythematous, edematous plaque with central ulceration (black necrotic core), rapidly affecting subcutaneous tissue, muscle, and bone. There are atypical presentations, including forms with eczematous-like lesions. Diagnosis must be prompt due to the accelerated progression of the disease. Clinical symptoms alone are insufficient, as they may be confused with other infections. Prioritized samples include nasal mucosa scrapings, sinus aspirates, bronchoalveolar lavage fluid, and biopsy of any necrotic tissue. Early diagnostic techniques such as direct observation with KOH or calcofluor staining are performed. Wide (5-15 µm in diameter), septate, and 45° angled branching hyphae may appear. Tissue samples can be taken, but results are often negative.[7]

The treatment of choice is amphotericin B (5-10 mg/kg/day for both children and adults), accompanied by surgical debridement and immune reconstitution. Once the patient is stabilized, treatment may be continued or switched to oral posaconazole or isavuconazole. The duration of treatment is not clearly established but typically lasts weeks until clinical resolution is achieved and no symptoms or signs of infection are present. SARS-CoV-2 causes a wide range of respiratory tract infections, from mild colds to severe respiratory distress syndrome. With the emergence of the new disease in 2019, known as severe acute respiratory syndrome SARS-CoV-2 and coronavirus disease 2019 (COVID-19), the world was forced to make drastic changes to daily routines, as this new virus presented with a previously fatal clinical picture.[2,7,8]

Transmission occurs from person to person through common routes, such as direct contact, aerosol transmission, or during medical procedures. Common forms include coughing, sneezing, inhalation of droplets, and contact with oral, nasal, and ocular mucous membranes. The virus is shed through the respiratory tract, saliva, feces, and urine. Viral load is higher and duration is also greater in patients with severe COVID-19. Clinical symptoms of SARS-CoV-2 vary greatly; the most common symptoms are fever, cough, and myalgia, while mild symptoms include sore throat, headache, chills, nausea, vomiting, diarrhea, and conjunctival congestion. COVID-19 is clinically classified into mild to moderate disease (non-pneumonia and pneumonia), severe disease (dyspnea, respiratory rate greater than 30/min, oxygen saturation below 93 %, PaO2/FiO2 ratio less than 300 and/or lung infiltrates in more than 50 % of the lung field within 24 to 48 hours), and critical disease (respiratory failure, septic shock, and/or multi-organ dysfunction/failure).[9,10]

Diagnosis was performed using virological detection through RT-PCR with swabs (nasopharyngeal, oropharyngeal), sputum, and feces, chest X-rays, and dynamic monitoring of inflammatory mediators such as cytokines. COVID-19 patients showed elevated blood levels of cytokines and chemokines such as interleukin (IL)-7, IL-8, IL-9, IL-10, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-alpha, and VEGFA.[9,11]

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As a new virus with a wide range of symptoms, patients with ARDS were treated with antiviral drugs and systemic corticosteroids, including neuraminidase inhibitors (oseltamivir, peramivir, zanamivir), ganciclovir, acyclovir, and ribavirin, as well as methylprednisolone. These treatments reduced the risk of death in patients with ARDS. Nucleoside analogs affecting the viral RNA structure were also used against a broad spectrum of RNA viruses, such as favipiravir, favilavir, ribavirin, remdesivir, galidesivir, and protease inhibitors. Treatments against malaria, such as chloroquine (CQ) and hydroxychloroquine (HCQ), were also used, along with cytokine-based therapies and extracorporeal membrane oxygenation.[9,11] Major pharmaceutical companies have developed vaccines, with currently 10 types produced by the following manufacturers: Pfizer/BioNTech, AstraZeneca/Oxford, Janssen, Moderna, Sinopharm, Sinovac, Bharat, Novavax, Casino, and Valneva.[12]

The review identified a wide range of studies addressing issues directly related to the relationship and development of mucormycosis in patients with COVID-19. Geographic variations in the prevalence of the infection were observed, and new findings were highlighted regarding the relationship between patient progression and the development of mucormycosis according to the patient's condition. Among the reviewed articles on mucormycosis related to COVID-19, it is suggested that this fungal infection can be a severe and potentially fatal complication of the disease. The most significant risk factors for COVID-19-associated mucormycosis (CAM) are poorly controlled type 2 diabetes mellitus and corticosteroid treatment.[13]

CAM most frequently presents as rhino-orbital-cerebral mucormycosis (ROCM), affecting the nose, eyes, and brain. Cases of pulmonary, cutaneous, and gastrointestinal mucormycosis have also been reported. Diagnosing CAM can be challenging, as symptoms are similar to those of other fungal and bacterial infections. Imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), can assist in confirming the diagnosis.[14,15]

The treatment of CAM is complex and requires a multidisciplinary approach. Initial treatment typically consists of intravenous antifungals, such as amphotericin B deoxycholate or posaconazole. In some cases, surgery may be necessary to remove infected tissue.[16] The mortality rate of CAM is high, even with treatment. In a study spanning 18 countries, the 30-day mortality rate was 58%. The reviewed articles provide the following recommendations for preventing CAM in patients with COVID-19:[16,17]

- Properly control type 2 diabetes mellitus.
- Avoid unnecessary use of corticosteroids.
- Be alert to signs and symptoms of CAM, such as headache, blurred vision, facial pain, blood-tinged cough, and skin lesions.

As observed in the literature, this article is one of the first to present mucormycosis as an opportunistic pathogen in COVID-19 infections. It discusses patient progression and the comorbidities and conditions that can develop. This information was provided after analyzing several previous research results. It details the high mortality of patients with mucormycosis as a secondary infection when COVID-19 is already present. Post-COVID-19 mucormycosis is common in India, especially among diabetics treated with corticosteroids. The triad of SARS-CoV-2, corticosteroids, and diabetes significantly increases the incidence of invasive maxillofacial mucormycosis. Rhino-orbital/rhino-cerebral mucormycosis is the most frequently reported infection. Mortality is higher in cases of COVID-19 with mucormycosis, complicating the pandemic landscape. Treatment includes surgical debridement and amphotericin B, with favorable outcomes in cases treated early.[18]

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Historically, mucormycosis is associated with a poor prognosis, but with COVID-19, early treatment has shown favorable results. Mortality is higher in patients with post-COVID-19 mucormycosis, highlighting the need for preventive measures and a risk-based approach.[19]

Rhino-orbital-cerebral mucormycosis (ROCM) is a common presentation, beginning in the nasal turbinates and aggressively spreading to surrounding structures. The fungal angioinvasion causes ischemia and tissue necrosis, with potential complications such as thromboembolism in nearby arteries and veins. Patients may experience a range of symptoms from facial pain and headache to proptosis, vision loss, and facial paralysis.[20,21]

The morbidity and mortality associated with mucormycosis in COVID-19 patients remain a significant global concern. As of the cutoff date of this review, there has been a significant increase in cases of COVID-19-associated mucormycosis (CAM) in various regions worldwide, with India, Iran, and Egypt having the highest prevalence, particularly in Gujarat and Maharashtra states in India.[20,22,23]

The prevalence of CAM is notably higher in patients with COVID-19 who have underlying risk factors, such as poorly controlled diabetes mellitus and diabetic ketoacidosis (DKA). Additionally, systemic corticosteroid administration, a common component in the treatment of severe COVID-19 patients, has also been identified as a precipitating factor for mucormycosis.[24] Regarding epidemiology, a significant increase in CAM cases has been observed since the onset of the pandemic. Cases have been reported in different regions, including the UK, the US, South America, Europe, the Middle East, and Asia, with India being the most affected, having a higher prevalence compared to other countries. The high regional prevalence in India may be attributed to factors such as the large diabetic population and specific environmental conditions like the humid tropical and subtropical climate.[25]

The role of ketoacidosis and free iron in the pathogenesis of mucormycosis has been highlighted, especially in diabetic patients who develop DKA. Acidosis in these patients can create an environment conducive to fungal growth, particularly Rhizopus oryzae, commonly associated with mucormycosis. Additionally, the presence of free iron in the serum of patients with DKA may contribute to the growth of Mucorales, as these fungi critically depend on acquiring iron from the host as a virulence factor.[24,25]

The interaction between COVID-19 and mucormycosis highlights the temporal increase in mucormycosis cases following a COVID-19 diagnosis. The combination of steroid therapy and the presence of diabetes mellitus significantly increases the risk of mucormycosis. Furthermore, the immune system impairment due to COVID-19, including lymphopenia and dysregulation of gamma interferon expression, may contribute to the patient's vulnerability to mucormycosis. Clinical manifestations of CAM vary depending on the site of involvement, with rhino-orbital-cerebral being the most common. Symptoms include orbital/facial pain, orbital/facial edema, vision loss, ptosis, nasal obstruction, among others. Pulmonary involvement has also been observed, with fever, cough, dyspnea, and hypoxia being the primary signs and symptoms.[26]

COVID-19–associated mucormycosis (CAM) is a severe opportunistic fungal infection primarily caused by species such as Rhizopus oryzae, Rhizopus microsporus, and Lichtheimia mucor. Its management relies on prompt antifungal therapy, with liposomal amphotericin B as the drug of choice, often combined with surgical debridement and correction of underlying risk factors, particularly uncontrolled diabetes and corticosteroid use. Despite these interventions, CAM continues to carry high morbidity and mortality, with regional variations in outcomes—mortality being lower in highly prevalent areas such as India. Early diagnosis remains challenging but is

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critical to improving survival, underscoring the need for ongoing research, surveillance, and preventive strategies to mitigate its impact.[27]

CONCLUSIONS

The COVID-19 pandemic has been accompanied by a marked rise in mucormycosis cases, especially in regions such as India, Iran, and Egypt, where patients with uncontrolled type 2 diabetes mellitus and those receiving corticosteroid therapy are most affected. The interplay between corticosteroid-induced hyperglycemia, viral ferritin release, and immunosuppression creates an environment highly conducive to fungal proliferation, particularly in individuals with diabetic ketoacidosis. Mucormycosis in this context represents a severe and life-threatening complication that demands rapid diagnosis and intervention. Standard management involves intravenous antifungal therapy, primarily liposomal amphotericin B, and surgical debridement when necessary. Despite these measures, mortality remains high, underscoring the urgent need for vigilant clinical management, preventive strategies, and continuous monitoring to improve patient outcomes.

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