




COVID-19 associated mucormycosis: the urgent need to reconsider the indiscriminate use of immunosuppressive drugs

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Invasive mycoses represent opportunistic infections occurring predominantly among highly immunosuppressed individuals, including those with advanced human immunodeficiency virus-associated immunosuppression, uncontrolled diabetes mellitus, drug-induced immunosuppression during transplantation, autoimmune disorders, or hematological malignancies. The overuse of high-dose glucocorticoids and the administration of highly immunosuppressive drugs such as inhibitors of the Janus kinase inhibitors or IL-6 receptor inhibitors to treat patients with the coronavirus disease 2019 (COVID-19) are responsible in part for the increasing number of life-threatening opportunistic infections identified in this patient population.^{1,2} In addition to the iatrogenic immunosuppression induced by these medications, there has been clear evidence from the onset of the COVID-19 pandemic that lymphopenia is a common laboratory finding, indicating some degree of immunological dysfunction in individuals with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.^{3,4}

Indeed, lymphopenia is a predictor of poor clinical outcome in the elderly with COVID-19.³ Furthermore, autopsy-based data demonstrate the paucity of inflammation identified during COVID-19 infection.⁵ When one compares the occurrence of viral pneumonia in patients with SARS (SARS-CoV-1), Middle-Eastern respiratory syndrome (MERS), and influenza, there are numerous data to suggest that the main pathologic process is disruption of the alveolar-capillary unit by viral-induced necrosis and apoptosis of the respiratory epithelium.⁶ The overuse of high-dose glucocorticoids in these viral infections is

not only of questionable benefit, but has been associated with increased mortality in the case of influenza.⁷⁻⁹ Based on currently available literature, the pathogenesis of viral pneumonia seen in patients with COVID-19 is not significantly different compared with that seen in SARS, MERS, and influenza, except for the increasing number of micro thrombosis or large embolism identified in autopsy studies in patients with COVID-19.⁵

The increasing number of recent case series of mucormycosis complicating COVID-19 patients in the United States,¹⁰⁻¹⁶ Austria,¹⁷ Brazil,¹⁸ Mexico,¹⁹ Italy,²⁰ France,²¹ Iran,²²⁻²⁴ and India,²⁵⁻³⁴ raises concerns regarding the misuse of immunosuppressive drugs in patients with COVID-19. Mucormycosis is a neglected mycosis which should be considered in the context of patients with COVID-19, in the same way as COVID-19 associated pulmonary aspergillosis, and it is possibly underreported. High doses of corticosteroids or their prolonged use should be balanced between the risk and benefit of *primum non nocere*. It is crucial to know the interaction between host, environment, SARS-CoV-2, and Mucorales to establish individual risk stratification and prevention measures, carry out rapid diagnosis, and offer timely treatment that may impact the morbidity and mortality of this deadly fungus.³⁵

As observed in the pandemic, the indiscriminate use of high-dose glucocorticoids or early corticosteroids use in patients with COVID-19 stems from some studies that evidenced benefits in certain specific clinical scenarios, such as those with severe disease needing oxygen or intubation, where its correct use may decrease fatal outcomes.³⁶ However, for those of us in the trenches

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caring for patients with COVID-19, the empiric overuse of corticosteroids has been associated with negative outcomes. Classically, uncontrolled diabetes mellitus, neutropenia, and corticosteroid therapy are known risk factors for mucormycosis.^{22,37} There is an urgent need to reconsider the careful use of these drugs in patients with severe COVID-19 due to the high prevalence of underlying comorbidities in these patients,^{11–13,25,28–30} including diabetes mellitus,^{13,16,19,26,28–30} hematological malignancies (i.e. acute myeloid leukemia),¹⁷ end-stage kidney disease,²⁷ and organ transplant recipients.¹⁵ A recent review of published cases found eight reports²⁷ where diabetes mellitus was the most common risk factor for development of mucormycosis. Three subjects had no risk factor other than glucocorticoid administration for severe COVID-19.²² Authors found that mucormycosis usually developed 10–14 days after hospitalization.²⁷ The combination of steroid therapy and diabetes mellitus increases the risk of mucormycosis mediated by hyperglycemia-induced immunosuppression.²² Immunosuppression in mucormycosis is majorly related to dysfunction in mononuclear and polymorphonuclear phagocytes in addition to increased oxidative and non-oxidative mechanisms. These changes are increased in severe COVID-19.^{38–40} Most of the published cases identified *Rhizopus* as the most frequent species.^{11,12,15,17,21,27,33,41} The occurrence of COVID-19-associated mucormycosis (CAM) in this group of patients may present with rhino-orbital involvement, but often involves other organs (i.e. pulmonary, gastrointestinal, intracranial), leading to fatal outcomes.^{12,13,18–20,23,28,30,42} Diagnosis of invasive aspergillosis, mucormycosis, and other opportunistic fungal infections occurs frequently during post-mortem examinations.^{17,22,39,43,44}

A recent case series of 18 patients with COVID-19 in India found that 16 developed mucormycosis, six of them with a fatal outcome (>37%).²⁸ Another series of 10 patients in India identified 10 patients with CAM, suggesting that this condition is more common than expected.²⁹ Treating physicians should have a high suspicion for CAM in patients with uncontrolled diabetes mellitus and severe COVID-19 presenting with rhino-orbital or rhino-cerebral syndromes.¹⁶ Regardless of the reported regional differences in the underlying causes, manifestations and treatment of mucormycosis is noted in studies throughout

Europe, Asia, and Latin America,⁴⁵ and, given the wide global distribution of the order Mucorales,^{41,46,47} CAM should be considered among the differential diagnosis of co-infections in patients with COVID-19. A prompt diagnosis and treatment should be established because of the angioinvasive character and rapid disease progression leading to a high mortality.^{48,49} This is especially true in India; with an increased incidence of COVID-19 cases, apparently thousands of CAM cases are reported. However, Nepal, Brazil, Colombia, the USA, and other severely affected nations should consider this fungal threat amid the pandemic. Also, it is essential to limit the dose and duration of high-dose dexamethasone as a treatment for COVID-19 in patients with a low likelihood of benefit or with an increased risk of complications (delayed presentation, or presence of uncontrolled diabetes mellitus).

The therapeutic approach during the COVID-19 pandemic should consider existing guidelines for mucormycosis management, such as those proposed by the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium.⁵⁰ Specific guidelines in the context of COVID-19 are needed,⁵¹ and new and updated COVID-19 guidelines should also include CAM as a diagnostic consideration.⁵² Upon suspicion of mucormycosis, appropriate imaging is strongly recommended to document the extent of the disease followed by a surgical assessment for debridement.⁵⁰ First-line treatment is high-dose liposomal amphotericin B. Intravenous isavuconazole and intravenous or delayed-release tablet posaconazole are recommended for de-escalation or maintenance therapy.^{53–57} Amphotericin B deoxycholate is advised against, given substantial toxicity, but may be the only option in resource-limited settings. Management of mucormycosis depends on recognizing disease patterns and on early diagnosis. Despite treatment, case-fatality rates due to mucormycosis during the pre-COVID-19 pandemic era were already high, ranging from 32% to 70%, according to organ involvement. However, in SARS-CoV-2 infection, the mortality may be even higher.⁵⁸

The prescription of immunosuppressing drugs can lead to life-threatening opportunistic infections in patients with COVID-19, and the lack of

substantial evidence for many of these therapies calls for an urgent reassessment of the current treatment guidelines for COVID-19, including monitoring for opportunistic fungal infections. The rationale and benefit of administering steroids in patients with COVID-19 needs continuous reappraisal to avoid the increasing number of iatrogenic deaths linked to steroid overuse in those with SARS-CoV-2 infection.

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We dedicate this Editorial to the memory of Dr. Francisco Miguel Marty, who died tragically in 2021. Dr. Marty is remembered as a gentle, well-rounded individual with extensive expertise in mucormycosis and other opportunistic infections, including mucormycosis in organ transplant recipients and patients with malignancies.

Author contributions

AJRM conceived the idea of the Editorial and drafted the first version. The rest of the authors contributed to subsequent versions. All authors read and approved the final submitted version.

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The authors declare that there is no conflict of interest.


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