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Letter

Antifungal Treatment of Mucormycosis Associated with COVID-19

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Mucormycosis is an angioinvasive fungal infection due to fungi of the order Mucorales. The prognosis from mucormycosis can be poor despite early diagnosis and aggressive therapy. The systematic review and meta-analysis by Muthu and colleagues [1] investigated the rate of mortality in patients with pulmonary mucormycosis. While there had been a significant decrease in the mortality rate over time, the recent (2010-2020) rate of mortality is still substantial, in which about one in two patients (49.8%; 95% confidence interval 43.2% to 56.3%) with pulmonary mucormycosis died from the disease. Yet, patients originated from the lower-middle-income countries had a higher mortality rate, in which about three in four patients (71.5%; 95% confidence interval 58.7% to 84.3%) with pulmonary mucormycosis died from the disease. Indeed, there has been a recent surge in the occurrence of mucormycosis in lower-middle-income countries, especially in India. As raised by Szarpak [2], the increased incidence with a fairly severe course of mycormycosis was reported in patients with a history of coronavirus disease 2019 (COVID-19) and received systemic corticosteroid therapy.

The presence of multiple risk factors in patients with COVID-19, along with the additional immunosuppression caused by systemic corticosteroids, predispose the occurrence of mucormycosis, which could negate the mortality benefits offered by systemic corticosteroids in this patient population [3]. Common risk factors include the presence of diabetes mellitus, particularly with ketoacidosis. Noteworthily, the management of patients with mucormycosis, which is considered rare before the COVID-19 pandemic, had not been optimal as described in a case report [4]. Optimal antifungal therapy is of utmost importance considering the substantial rate of mortality.

Intravenous amphotericin B is the drug of choice for initial therapy of mucormycosis; a lipid formulation of amphotericin B (liposomal amphotericin B or amphotericin B lipid) is preferred to reduce the risk of nephrotoxicity. In a meta-analysis of five randomized trials, the incidence of nephrotoxicity was significantly lower with liposomal amphotericin B compared with amphotericin B deoxycholate (15% versus 33%; relative risk = 0.48; 95% confidence interval 0.36 to 0.64) [6]. The usual starting dose for amphotericin B is 5 mg/kg daily, which can be increased up to 10 mg/kg daily to control the infection.

While amphotericin B is generally considered the first-line agent for the treatment of mucormycosis. Posaconazole or isavuconazole is used as step-down therapy for patients who have responded to amphotericin B. Therefore, once patients respond and are deemed suitable for discharge, they could be initiated with either one of the aforementioned antifungal agents. Posaconazole and isavuconazole are broad-spectrum azoles that are active in vitro against the pathogens of mucormycosis. A systematic review [7] of 96 case reports of patients with mucormycosis reported a response rate of 72.9% with posaconazole. On the other hand, isavuconazole has been evaluated in a multicenter open-label single-arm study that included a total of 37 patients with mucormycosis [8]. When the researchers compared patients, who received isavuconazole with their contemporary counterparts who received amphotericin B (the majority received a lipid formulation), it was observed that the weighted all-cause mortality was similar

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in those who received isavuconazole (33%) and in those who received amphotericin B followed by posaconazole (41%). Posaconazole (delayed-release tablets) can be dosed at 300 mg every 12 hours on the first day, then 300 mg once daily, with no dosage adjustment necessary for patients with a decline in renal function. Whereas isavuconazole can be loaded at a dose of 200 mg every 8 hours for 2 days, followed by a maintenance dose of 200 mg orally once daily starting 12 to 24 hours after the last loading dose.

Antifungal therapy should be continued until clinical resolution of the signs and symptoms, as well as resolution of radiographic signs of mucormycosis. Perhaps in the context where there is a widespread outbreak of mucormycosis, the use of systemic corticosteroids should be more judicious in patients at high risk, such as those with diabetes, keeping in mind that systemic corticosteroids could aggravate hyperglycemia. The use of intravenous pulse methylprednisolone therapy for as short as three days to limit its side effects can be considered [9]. Besides, baricitinib, a Janus kinase inhibitor, which has proven mortality benefits, can be considered as an alternative to systemic corticosteroids in patients with COVID-19 [10].

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