Letter to the Editor

A look into the relationship between outdated coronavirus disease 2019 (COVID-19) treatment protocols and the overwhelming rise of mucormycosis in COVID-19 patients in India

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To the Editor—India, the second most-affected country by coronavirus disease 2019 (COVID-19), recorded one of the worst second waves across the world, with >400,000 daily cases reported in early May 2021. In addition, the second wave brought with it a dramatic increase in mucormycosis cases amongst recovering and active COVID-19 patients. A recent update shows that by June 2021 India had recorded >40,000 mucormycosis cases, of whom 35,000 suffered from COVID-19.

Mucormycosis is a rare but serious angioinvasive condition caused by a group of ubiquitous fungi called Mucormycetes, and it mainly affects immunocompromised individuals. Mucormycosis has an aggressive nature, requiring early diagnosis and treatment. India, often called the global capital of mucormycosis, had an estimated prevalence 70 times higher than the global average even prior to the COVID-19 pandemic. However, with the arrival of the second wave, India recorded an unprecedented rise in mucormycosis cases among COVID-19 patients, far exceeding the global national average. On July 14, 2021, the number of mucormycosis cases exceeded that of active COVID-19 cases in Delhi, the nation’s capital.

Although an official treatment protocol for COVID-19 was published by the Indian Council of Medical Research, protocols among different states varied greatly, with certain states adopting different treatment guidelines. For example, the treatment guidelines published by the Health and Family welfare of the state of Tamil Nadu included drugs such as azithromycin and zinc for mild COVID-19 cases, despite low certainty of evidence. These medications were absent from the treatment protocol published by the Indian Council of Medical Research.

Despite official treatment protocols using evidence-based therapies, doctors across the country have typically prescribed a cocktail of medications in high doses including azithromycin, doxycycline, vitamin C, vitamin D, zinc, and inhaled budesonide/dexamethasone, despite the lack of available evidence-based research for some of these medications. This trend of blanket treatment, coupled with the rising incidence of self-medication, due to the wide availability of these medications and poor regulation of prescription-based drugs, may have played a large part in the rise of mucormycosis cases.

Among the different medications prescribed by healthcare professionals, great attention has been given to zinc as a contributory factor in the rise of mucormycosis cases. Zinc has typically been prescribed to patients in India in high doses of 50 mg for a course of 5 days or more. Although there is no evidence of a direct relationship between zinc and mucormycosis, Staats et al describe the importance of zinc in the fungal metabolism, observing that zinc starvation places increased stress on fungal development by interfering with zinc-binding proteins that act as transcription factors. Furthermore, Leonardelli et al described the increased efficacy of amphotericin B and posaconazole against mucormycosis when paired with zinc chelators, thereby demonstrating the vital role of zinc in the growth and development of Mucormycetes.

Several experts have questioned the use of antibiotics, such as azithromycin, which is prescribed in India in doses of 500 mg, thrice daily for 3 days for the treatment of even mildly ill COVID-19 patients. Antibiotics offer little to no benefit and may even be counterproductive. Also, undue use of antibiotics may disturb the normal commensals that would otherwise protect from opportunistic infections such as mucormycosis. A randomized control trial by the RECOVERY collaborative group10 studied the use of azithromycin in COVID-19 patients across 176 hospitals in the United Kingdom and determined that azithromycin did not improve survival in COVID-19 patients. In addition, the use of such antibiotics has also been questioned by Dr V.P. Pandey, who studied 210 COVID-19 patients with mucormycosis at MGM Medical College in Indore, India.11 Antibiotics had been used by 100% of the patients.

Perhaps, the most important factor contributing to the rise of COVID-19-associated mucormycosis in India is the nonchalant use of steroids, even across the mildest cases of COVID-19. Glucocorticoid induced hyperglycemia and immunosuppression, together with COVID-19-induced hyperglycemia, lymphopenia, and immune dysregulation (causing decreased T lymphocytes, CD4+ and CD8+ T cells),12 create a favorable environment for the growth of Mucormycetes. These factors are enhanced by the increased use of steroids in large doses, even across the mildest COVID-19 cases, due their easy over the counter availability in India. Furthermore, the current Indian guidelines regarding steroid use advise 0.5–1 mg/kg/day of methylprednisolone in moderate cases and 1–2 mg/kg/day in severe cases of COVID-19. This dosage is far higher than the recommendation by the National Institute of Health, which is
6 mg/day for a maximum of 10 days and only for those on assistive ventilation or supplemental oxygen therapy.12

Steam inhalation and the use of nebulizers are also suspected to be contributory agents to the rise in COVID-19–associated mucormycosis cases, due to poor quality of water and unsterilized equipment used in such procedures. Such procedures can facilitate the transport of fungal spores into the respiratory tract via inhalation, where the spores can develop. Furthermore, steam inhalation can also cause scald injuries13 to the respiratory tract, thereby reducing the efficacy of local immune responses, which in turn facilitates the development of foreign pathogens. However, despite advisories against steam inhalation due to lack of evidence citing its benefits, it has been used widely as routine treatment across Indian households.

Hence, COVID-19 treatment guidelines need to be updated, and uniform compliance of these guidelines needs to be ensured across the country to prevent dire complications such as mucormycosis. This is especially important in a country like India, where resources are scarce and life-saving medications for mucormycosis, such as amphotericin B, have been in very short supply in recent months and the cost of such therapies far exceeds the affordability of the common man in India.14

Acknowledgments.

Financial support. No financial support was provided relevant to this article.

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

References


