Received: 20 May 2021 | Revised: 27 June 2021 | Accepted: 19 July 2021

DOI: 10.1002/ddr.21862

COMMENTARY

DRUG DEVELOPMENT RESEARCH WILEY

Emerging cases of mucormycosis under COVID-19 pandemic in India: Misuse of antibiotics

Gaurav Gupta[1] | Roshan S.[2] | Yogendra Singh[3] | Lakshmi Thangavelu[4] | Sachin Kumar Singh[5] | Harish Dureja[6] | Dinesh Kumar Chellappan[7] | Kamal Dua[8]

[1]School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

[2]Deccan School of Pharmacy, Osmania University, Hyderabad, India

[3]Department of Pharmacology, Maharishi Arvind College of Pharmacy, Ambabari Circle, Jaipur, India

[4]Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical Sciences, Saveetha University, Chennai, India

[5]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

[6]Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

[7]Department of Life Sciences, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia

[8]Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, New South Wales, Australia

Correspondence
Gaurav Gupta, School of Pharmacy, Suresh Gyan Vihar University, Mahal Road, Jagatpura, Jaipur, 302017, India.
Email: gauravpharma25@gmail.com

Abstract

COVID-19's second wave had a significant impact on India, on May 7, 2021, the largest daily recorded case count was a little more than 4 million, and it has since fallen. Although the number of new cases reported has dropped, during the third week of May 2021, India accounted for about 45% of new cases identified globally and around 34% of deaths. As India maintains its present level of stability, a new urgent threat has emerged in the form of coronavirus-associated mucormycosis. Mucormycosis, an acute and deadly fungal infection caused by Mucorales-related fungal species, is a fungal emergency with a particularly aggressive propensity for contiguous spread, associated with a poor prognosis if not properly and immediately identified, and treated. Mucormycosis, sometimes referred to as the "black fungus," has increased more rapidly in India during the second wave of COVID-19 than during the first wave, with at least 14,872 cases as of May 28, 2021. Uncontrolled diabetic mellitus (DM) and other immunosuppressive diseases such as neutropenia and corticosteroid treatment have traditionally been identified as risk factors for mucormycosis. Therefore, the use of glucocorticoids or high doses of glucocorticoids in mild COVID-19 cases (without hypoxemia) should be avoided. In addition, drugs that target the immune pathway, such as tocilizumab, are not recommended without clear benefits.

KEYWORDS
black fungus, COVID-19, mucormycosis, SARS-CoV-2, steroids

In December 2019, the first case of SARS-CoV-2 (COVID-19) coronavirus disease was identified in Wuhan, China. The disease spread rapidly and was announced as a Public Health Emergency of International Importance on 30 January 2020. On March 11, 2020, the World Health Organization declared it a pandemic. COVID-19, which is caused by the SARS-CoV-2 virus, has been linked to a variety of opportunistic bacterial and fungal diseases (Kubin et al., 2021). Both Aspergillosis and Candida have been identified as the primary fungal infections associated with co-infection in COVID-19 patients (Song et al., 2020). Recently, many instances of mucormycosis in persons living with COVID-19 have been documented globally, most notably in India. COVID-19 associated individuals are prone to serious opportunistic infections due to related comorbidities including COPD and diabetes and immunosuppressed conditions like ventilation, corticosteroid therapy, and ICU stay. As India continues to be infected with around 350,000 new infections every day, the second wave of COVID-19 is shocking, leading to a massive increase in the number of cases requiring strong medication. The disease rate is ~0.14 cases per 1000 people, which is ~80 times the prevalence rate. Infection with COVID-19 is linked to a fungal infection. Mucormycosis, an acute and deadly fungal infection caused by Mucorales-related fungal species, is a fungal emergency with a particularly aggressive propensity for contiguous spread, associated with a poor prognosis if not properly and immediately identified and treated. Uncontrolled diabetic mellitus (DM) and other immunosuppressive diseases such as neutropenia and corticosteroid treatment have traditionally been identified as risk

factors for mucormycosis. Inhalation of spores and/or seeding onto the airways or any susceptible epithelium required for the spread of mucormycosis; using host conditions such as hyperglycemia, ketoacidosis, iron overload, and neutropenia to germinate into angioinvasive hyphae that cause endothelium damage; resulting in local hemorrhaging, thrombosis, and necrosis, as well as eventual spread to numerous organs (Ahmadikia et al., 2021; Cornely et al., 2019; Salehi et al., 2020).

Although rare, the infection has been around for decades, but it only affects people whose health is compromised by the use of steroids and whose immune system is significantly weakened. Increased cases of mucormycosis in COVID-19 patients are prevalent, primarily due to increased use of steroids such as dexamethasone, especially among diabetics. Not everyone is susceptible to black fungus, but unchecked and unsupervised use of steroid therapy can often exacerbate the situation, even for non-risk patients. Supportive care plays an important role in the management of COVID-19 in the absence of effective vaccines and antiviral therapies. Glucocorticoids and perhaps remdesivir are the only drugs that have proven beneficial in COVID-19 (Jain et al., 2020; Rajendra Santosh et al., 2021). Glucocorticoids are inexpensive and widely available and have been shown to reduce mortality in patients with COVID-19 hypoxemia. Nevertheless, glucocorticoids can increase the risk of secondary infections. In addition, the combination of virus-induced immunomodulatory dysfunction and immunomodulatory drugs such as tocilizumab may further increase the risk of infection in patients with COVID-19 (Revannavar et al., 2021; Somasekharan Nair Rajam et al., 2020).

A case of COVID-19 infection with multiple infections of nasal orbital zygomycosis along with ketoacidosis has been identified in a newly diagnosed diabetic patient. Reduced phagocytic activity, transferrin replacement increases iron availability in diabetic ketoacidosis and fungal heme oxygenase enzyme that facilitates iron absorption for the fungal metabolism are the pathogenic pathways implicated in fungal aggression. In the case mentioned for extreme COVID-19 coinfection with fungi, cell count reveals a gradual decrease in lymphocytes while a progressive rise in the number of neutrophils and white blood cells. It has been hypothesized that infection with SARS-CoV-2 can have an effect on CD4 + and CD8 + T cells, to play a significant role in the pathophysiology of COVID-19 infection (Garg et al., 2021; Saldanha et al., 2021). In severe COVID-19 cases, the total number of T cells and lymphocytes decreases and has been linked to the most negative outcomes. T cells specific for Mucorales, like CD4 + and CD8 +, produce cytokines such as IFN-γ and IL-4, IL-10, IL-17, and fungal filaments that cause damage. According to Sharma et al., such unique T cells are only present in patients with invasive mycosis, and that they may be useful surrogate diagnostic markers for invasive mycosis. Lymphopenia can raise the chance of transmitting invasive mucormycosis, although an increase in lymphocyte count can be beneficial to the adaptive immune system and induce T cell development specific for Mucorales, which can aid in the control of the invasive infection (Sarkar et al., 2021).

There are many reports showing changes in cell-mediated immunity involving phagocytosis, chemotaxis, and cytokine secretion in diabetic patients. Diabetes has been associated with changes in the components of the innate immune system. Diabetics have lower natural killer cell function and more pro-inflammatory M1 macrophages are present. In addition, T cell activity is distorted (Chowdhury & Barooah, 2020; Dyer, 2021). The severity of the patient's illness is due to the host's reaction as well as the viral infection. Blood sugar levels that are too high can also inhibit antiviral responses. About COVID-19, the progression of severe disease is explained by a long-term hyperinflammatory condition and a delayed IFN-γ response with decreased CD4 and CD8 cell numbers. Irrespective of endothelial cell activity, in diabetic patients, the initial delay in IFN-γ response, together with the hyperinflammatory response, can intensify the "cytokine storm" and make COVID-19 more serious (Sen, Honavar, et al., 2021). Endothelial dysfunction is associated with elevated endothelial inflammation, vascular lesions, and vasoconstriction. Diabetics have an increased risk of the endothelium in some organs. Vasoconstriction-induced tissue edema, organ ischemia, and procoagulant states may result from changes in vascular tone. Finally, the dysregulated immune cell population and activity observed in diabetics play an important role in exacerbating severity (Bair et al., 2021). The Indian subcontinent case series reported six cases of rhino-orbital-encephalomycosis after COVID-19 infection. The average time from the COVID-19 diagnosis to the onset of zygomycosis symptoms was 15.6 ± 9.6 days. Hyperglycemia control, early treatment with liposomal amphotericin B, and surgery are all necessary components of effective mucormycosis management (Sen, Lahane, et al., 2021). The development of mucormycosis may be due to the use of glucocorticoids, suggesting the need for their wise use. Therefore, the use of glucocorticoids or high doses of glucocorticoids in mild COVID-19 cases (without hypoxemia) should be avoided. In addition, drugs that target the immune pathway, such as tocilizumab, are not recommended without clear benefits.

In conclusion, although the complexity of COVID-19 necessitates that doctors treating patients make choices about a range of treatments, basic recommendations for the use and avoidance of specific therapies should guarantee that evidence-based, quality-controlled interventions are reasonably consistent. Self-medication and interventions might be strongly prohibited. A set of minimum criteria for all the organizations that care for these individuals may be created.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing, not available-no new data generated

ORCID

Gaurav Gupta https://orcid.org/0000-0001-7941-0229

REFERENCES

Ahmadikia, K., Hashemi, S. J., Khodavaisy, S., Getso, M. I., Alijani, N., Badali, H., Mirhendi, H., Salehi, M., Tabari, A., Mohammadi Ardehali, M., Kord, M., Roilides, E., & Rezaie, S. (2021). The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated

mucormycosis versus COVID-19 associated mucormycosis. *Mycoses*, *64*, 798–808. https://doi.org/10.1111/myc.13256

Bair, E., Stillinger, T., Rittger, K., & Skiles, M. (2021). COVID-19 lockdowns show reduced pollution on snow and ice in the Indus River Basin. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(18), e2101174118. https://doi.org/10.1073/pnas.2101174118

Chowdhury, P., & Barooah, A. K. (2020). Tea bioactive modulate innate immunity: In perception to COVID-19 pandemic. *Frontiers in Immunology*, *11*, 590716. https://doi.org/10.3389/fimmu.2020.590716

Cornely, O. A., Alastruey-Izquierdo, A., Arenz, D., Chen, S. C. A., Dannaoui, E., Hochhegger, B., Hoenigl, M., Jensen, H. E., Lagrou, K., Lewis, R. E., Mellinghoff, S. C., Mer, M., Pana, Z. D., Seidel, D., Sheppard, D. C., Wahba, R., Akova, M., Alanio, A., al-Hatmi, A. M. S., … Chakrabarti, A. (2019). Global guideline for the diagnosis and management of mucormycosis: An initiative of the European Confederation of Medical Mycology in cooperation with the mycoses study group education and research consortium. *The Lancet Infectious Diseases*, *19*(12), e405–e421. https://doi.org/10.1016/s1473-3099(19)30312-3

Dyer, O. (2021). Covid-19: India sees record deaths as "black fungus" spreads fear. *BMJ*, *373*, n1238. https://doi.org/10.1136/bmj.n1238

Garg, A., Ghoshal, U., Patel, S. S., Singh, D. V., Arya, A. K., Vasanth, S., Pandey, A., & Srivastava, N. (2021). Evaluation of seven commercial RT-PCR kits for COVID-19 testing in pooled clinical specimens. *Journal of Medical Virology*, *93*(4), 2281–2286. https://doi.org/10.1002/jmv.26691

Jain, V. K., Iyengar, K., Vaish, A., & Vaishya, R. (2020). Differential mortality in COVID-19 patients from India and western countries. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, *14*(5), 1037–1041. https://doi.org/10.1016/j.dsx.2020.06.067

Kubin, C. J., McConville, T. H., Dietz, D., Zucker, J., May, M., Nelson, B., Istorico, E., Bartram, L., Small-Saunders, J., Sobieszczyk, M. E., Gomez-Simmonds, A., & Uhlemann, A.-C. (2021). Characterization of bacterial and fungal infections in hospitalized patients with coronavirus disease 2019 and factors associated with health care-associated infections. *Open Forum Infectious Diseases*, *8*(6), 1–10. https://doi.org/10.1093/ofid/ofab201

Rajendra Santosh, A. B., Muddana, K., & Bakki, S. R. (2021). Fungal infections of Oral cavity: Diagnosis, management, and association with COVID-19. *SN Comprehensive Clinical Medicine*, *3*, 1–12. https://doi.org/10.1007/s42399-021-00873-9

Revannavar, S. M., Supriya, P. S., Samaga, L., & Vineeth, V. K. (2021). COVID-19 triggering mucormycosis in a susceptible patient: A new phenomenon in the developing world? *BML Case Reports*, *14*(4), e241663. https://doi.org/10.1136/bcr-2021-241663

Saldanha, M., Reddy, R., & Vincent, M. J. (2021). Title of the article: Paranasal Mucormycosis in COVID-19 patient. *Indian J Otolaryngol Head Neck Surg*, 1–4. https://doi.org/10.1007/s12070-021-02574-0

Salehi, M., Ahmadikia, K., Badali, H., & Khodavaisy, S. (2020). Opportunistic fungal infections in the epidemic area of COVID-19: A clinical and diagnostic perspective from Iran. *Mycopathologia*, *185*(4), 607–611. https://doi.org/10.1007/s11046-020-00472-7

Sarkar, S., Gokhale, T., Choudhury, S. S., & Deb, A. K. (2021). COVID-19 and orbital mucormycosis. *Indian Journal of Ophthalmology*, *69*(4), 1002–1004. https://doi.org/10.4103/ijo.IJO_3763_20

Sen, M., Honavar, S. G., Sharma, N., & Sachdev, M. S. (2021). COVID-19 and eye: A review of ophthalmic manifestations of COVID-19. *Indian Journal of Ophthalmology*, *69*(3), 488–509. https://doi.org/10.4103/ijo.IJO_297_21

Sen, M., Lahane, S., Lahane, T. P., Parekh, R., & Honavar, S. G. (2021). Mucor in a viral land: A tale of two pathogens. *Indian Journal of Ophthalmology*, *69*(2), 244–252. https://doi.org/10.4103/ijo.IJO_3774_20

Somasekharan Nair Rajam, S., Neenthamadathil Mohandas, K., Vellolipadikkal, H., Viswanathan Leena, S., Kollery Suresh, V., Natakkakath Kaliyathan, R., Sreedharan Nair, R., Lankalapalli, R. S., & Mullan Velandy, R. (2020). Spice-infused Palmyra palm syrup improved cell-mediated immunity in Wistar albino rats. *Journal of Food Biochemistry*, *44*(11), e13466. https://doi.org/10.1111/jfbc.13466

Song, G., Liang, G., & Liu, W. (2020). Fungal co-infections associated with global COVID-19 pandemic: A clinical and diagnostic perspective from China. *Mycopathologia*, *185*(4), 599–606. https://doi.org/10.1007/s11046-020-00462-9

How to cite this article: Gupta, G., S., R., Singh, Y., Thangavelu, L., Singh, S. K., Dureja, H., Chellappan, D. K., & Dua, K. (2021). Emerging cases of mucormycosis under COVID-19 pandemic in India: Misuse of antibiotics. *Drug Development Research*, *82*(7), 880–882. https://doi.org/10.1002/ddr.21862