Antifungal Drugs Shortage in India amidst Looming Increase in Invasive Fungal Infections among COVID-19 Patients: An Impending Crisis

Behram Khan Ghazi,MBBS[1]; Usman Zahid,MBBS[1]; Muhammad Abdullah Usman,MBBS[2]; Zohra Kazmi,MBBS[3]; Reem Hunain,MBBS[4]; Mehr Muhammad Adeel Riaz,MBBS[5]; Osman Kamal Osman Elmahi,MBBS[6]; Mohammad Yasir Essar,BDS[7]; Mohammad Mehedi Hasan,BSc[8]

[1]*Punjab Medical College, Faisalabad, Pakistan; Faisalabad Medical University, Faisalabad, Pakistan*
[2]*Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan*
[3]*Jinnah Medical and Dental College, Karachi, Pakistan*
[4]*Kasturba Medical College, Manipal, India*
[5]*Punjab Medical College, Faisalabad, Pakistan*
[6]*Faculty of Medicine, Ibn Sina University, Khartoum, Sudan; Oli Health Magazine Organization, Sudan*
[7]*Kabul University of Medical Sciences, Kabul, Afghanistan*
[8]*Mawlana Bhashani Science and Technology University, Tangail, Bangladesh*

Abstract

The widespread prevalence of fungal infections in the second wave of COVID-19 pandemic could be owed to ubiquitous and injudicious use of steroids and immunosuppressive nature of the virus. However, these fungal infections also meant increased use of antifungal drugs, hence endangering their supply. Amphotericin B is the first line drug for mucormycosis which was declared as an epidemic in India during the second wave. With the increasing demand of the drug, came challenges to manufacture and supply large quantities of the drug and exploitation by creating a black market and spread of false information and imprudent usage. It is of utmost importance to be prepared with adequate supply all over the nation and implementing safety regulations in manufacturing and supply of large quantities of drugs during the demanding times and make them accessible at a reasonable rate.

Keywords: Antifungal drugs, shortage, India, mucormycosis, Government policy

Background

The COVID-19 pandemic has affected humanity in unprecedented ways. The SARS-CoV-2 quickly spread throughout the world from its origins in China due to its higher reproductive number, hence making it more transmissible [1]. Extra pulmonary manifestations of the virus are now well established, with gastrointestinal, renal, dermatological, and neurological presentations being the other systems being affected by it [2].

As the pandemic has led to devastating effects over entire world, India has also been a major culprit in a way that it affected India tremendously and led to development of severe fungal infections post treatment during the second wave observed between May-June 2021 [3–5].

Corresponding author: Mohammad Mehedi Hasan, MBBS
Department of Biochemistry and Molecular Biology
Faculty of Life Science, Mawlana Bhashani Science and Technology University; Tangail, 1902, Bangladesh
Email: mehedi.bmb.mbstu@gmail.com

Mucormycosis, commonly known as the "black fungus" was predominant and transmitted widely during the second wave of COVID-19 in India as compared to the first wave. With at least 3726 cases of mucormycosis in patients with active and recovered COVID-19, the state of Gujarat reported the highest number of cases, followed by the state of Maharashtra [3,4]. Despite the fact that no official figures on mucormycosis in COVID-19 cases were released by the Union Health Ministry in the first wave of COVID-19, there were approximately 71 percent of global cases of mucormycosis reported in COVID-19 patients based on published literature from December 2019, to the beginning of April 2021 [6].

The overuse of steroids in the treatment of COVID-19, combined with the virus's immunosuppression, resulted in the emergence of this opportunistic fungal infection [7]. Since Indi holds a large diabetic population, uncontrolled diabetes and long-term stays in the intensive care unit are also the most common causes pertaining to the rise of mucormycosis in COVID-19 patients, with estimated prevalence of about 140 per million population [3,8]. More than 45,432 cases and 4252 deaths due to mucormycosis were reported till 15th July 2021 which were either among COVID-19 infected patients or in patients who had recovered from COVID-19 [9].

Although cases of mucormycosis were reported during the first wave, cases during the second wave became more prevalent, prompting state governments to declare this as an epidemic

DOI: https://doi.org/10.24926/iip.v13i2.4480

amidst the pandemic. The risk of the white fungus Aspergillosis, which is thought to be even deadlier than the black fungus, also was on the rise with a few cases reported in India [10]. Soon there were cases of more lethal 'white fungus' infection traced in Bihar.

Many developing countries across the globe, including India have recorded spiked incidence rates of invasive fungal infections. The incidence of Candida spp. Yeast infections is rising in the Indian subcontinent, with multidrug resistance present in up to 12% of Candida isolates. Excessive consumption of antifungal agents is also a current threat to antifungal stewardship in India, as *Candida spp.* isolates demonstrate decreasing susceptibility to amphotericin B - *C. tropicalis* and *C. albicans* isolates in India demonstrated minimum inhibitory concentrations of 29.2% and 16.8% respectively [11].

This observation is also solidified by the difficulty of their early diagnosis, which is paramount to successful patient outcomes, leading to inappropriate antifungal treatment regimens and increasing emergence of antifungal resistance in yeasts and mycelial fungi [11]. In addition, patient healthcare requirements are met by high out-of-pocket expenditure of households, with approximately 40 million people falling below the poverty line as a result [12]. In this context, this article aims to discuss the shortage of antifungal drugs in India during the pandemic and the government strategies addressing fungal infections.

Government Efforts and Role of Indian Pharmaceutical Industry

On 21 May 2021, mucormycosis was declared a notifiable disease under Epidemic Disease Act 1897, and all government and private hospitals were instructed to report every suspected and confirmed case of mucormycosis to the Union Health Ministry [13]. The government diversified healthcare bodies to ensure well-regulated use of steroids in the treatment of COVID - 19, and proper monitoring of glycemic index in diabetic patients avoiding these risk factors so as to avoid emergence of new secondary fungal infections.

The Ministry of Health & Family Welfare and Indian Council for Medical Research (ICMR) issued an advisory for proper identification, screening, diagnosis, and management of fungal infections [14]. The Union Health Ministry instructed all the state and union territory hospitals to establish Hospital Infection Control Committee and Implement Infection Control Program (IPC) in all the healthcare facilities in a manner conforming with national guidelines for infection & control in healthcare facilities, so to nexus on enactment of (i) Infection Prevention Control Manuals' in all the hospitals, (ii) Antimicrobial usage guidelines,(iii) risk assessment & management, (iv) educational programs, (v) planning, monitoring, & implementation of plan of action to halt the emerging cases of secondary fungal infections.

The Union Health Ministry along with the Department of Pharmaceuticals and the Ministry of External Affairs recommended domestic manufacturers to build up the production with a target of 1,63,752 vials of Amphotericin B in the month of May 2021, which was further anticipated to increase to 2,55,114 vials in June 2021 so to overcome the supply-demand disparity as per 'Whole of Government Approach' [15]. Additionally, 3,63,000 vials in May and 3,15,000 vials in June were imported from the supporting foreign countries, thereby increasing the overall nationwide availability of Amphotericin B injections to 5,26,752 in May and 5,70,114 in June 2021 [16].

Earlier, only five pharmaceutical companies namely Bharat Serum & Vaccine Ltd, Sun Pharma Limited, Lifecare Innovations, Cipla Limited, BDR Pharmaceuticals Limited in addition to Mylan Labs USA, manufactured Amphotericin B in India. The government of India issued incense to five more companies namely NATCO Pharmaceuticals, Emcure Pharmaceuticals, Lyca, alembic Pharma, and Gufic Biosciences Limited. These companies were targeted to produce 1,11,000 vials per month collectively [15]. The Union Health Ministry along with the Department of Pharmaceuticals in collaboration with the Ministry of External Affairs, the Health Ministry also put its efforts to look for other global sources to import the medication [15].

The Amphotericin B injections were restricted to be exported with an immediate effect from June 1, 2021 [16]. To make certain of the equitable distribution of drugs among healthcare bodies, the government also used the approach of 'Survey Based Allocations' through data collected from individual States and union territories to get maximum benefit from available stock [10]. Despite all such measures, the shortage of antifungal drugs has been a greatest danger to the already exhausted and overburdened healthcare system of India amid the annihilating second wave of COVID-19.

Implications

India faced an alarming shortage of antifungal drugs which are used in the treatment of Mucormycosis also known as Black Fungus during the second COVID-19 wave [17]. Although Amphotericin B is available in several forms, one form is a lyophilized form of Amphotericin B which is the most effective and commonly used drug in the treatment of Mucormycosis. A shortage of two raw materials has hit the production cycle. The first is the active pharmaceutical ingredient (API) Amphotericin B, that is mandatory for the production of two major forms of the drug i.e., "liposomal and plain form". The second raw material the production of liposomal Amphotericin B is purified synthetic lipids which is facing shortage in production due high demand globally for mRNA vaccine manufacturing.

Despite the government policy of increasing the production of the drug, the supply could not catch up to the demand in the market. There was 300 per cent increase in demand for

DOI: https://doi.org/10.24926/iip.v13i2.4480

antifungal drugs during the second wave. As these drugs were not available for sale in the open market, profiteers took advantage and started black marketing of these life-saving drugs. There was a significant hike in the prices. With people procuring these drugs at an unimaginable price, there was an exploitation of common people with black marketing getting out of control [18].

Therefore, with an increasing number of black and white fungal infections, the demand for antifungal drugs particularly Amphotericin B, which is considered the only suggested and effective in treating mucormycosis, increased conspicuously leading to acute shortage of the drug.

Recommendations and Conclusion

With cases of Mucormycosis progressively increasing in India, it is essential to take measures to alleviate the occurrence. In order to address the shortage, additional organizations must be looked into to manufacture the antifungal drug Amphotericin B and augment safe and easy import by the government. Innovative research is of importance to identify effective drugs and alternative treatment modalities. There is also the need for promotion and practice of antibiotic stewardship. Promoting local pharmaceutical production is also essential. With exponential demand overburdening the pharmaceutical companies, duty-free imports should be implemented to guarantee a sufficient stock and supply of drugs. Establishing a national database of mucormycosis incidences will also assist in keeping a track and mapping the supply of antifungal agents across the country in order to minimize excessive supply. The antifungal drugs are out of supply not only due to its scarcity but have also been found costly amid this critical stage. With pandemics still looming, it is imperative to establish guidelines to regulate effective manufacturing, import, distribution in order to prepare ourselves for any future outbreak.

The opinions expressed in this paper are those of the authors.

Acknowledgments: Not applicable.
Author Contributions: All the authors wrote the paper and contributed substantially to the manuscript. All authors read and approved the final manuscript.
Funding: No external funding was used in this study.
Availability of data and materials: Not applicable.
Ethics approval and consent to participate: Not applicable.
Conflict of Interests: The authors declare that there is no conflict of interests.

References

1. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020;382(12):1177-1179. doi:10.1056/NEJMC2001737
2. Moro E, Priori A, Beghi E, et al. The international European Academy of Neurology survey on neurological symptoms in patients with COVID-19 infection. *Eur J Neurol*. 2020;27(9):1727-1737. doi:10.1111/ENE.14407
3. Ghazi BK, Rackimuthu S, Wara UU, et al. Rampant Increase in Cases of Mucormycosis in India and Pakistan: A Serious Cause for Concern during the Ongoing COVID-19 Pandemic. *Am J Trop Med Hyg*. 2021;1(aop). doi:10.4269/AJTMH.21-0608
4. Rocha ICN, Hasan MM, Goyal S, et al. COVID-19 and mucormycosis syndemic: double health threat to a collapsing healthcare system in India. *Trop Med Int Heal*. 2021;26(9):1016-1018. doi:10.1111/TMI.13641
5. Ghosh S, Patelia S, Hasan MM, Ghosh A, Jain S, Patel T. Drug resistant White fungus: another catastrophic fungus emergence amidst COVID-19 in India. *Pathog Glob Health*. 2021. doi:10.1080/20477724.2021.1960762
6. John TM, Jacob CN, Kontoyiannis DP. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. *J Fungi 2021, Vol 7, Page 298*. 2021;7(4):298. doi:10.3390/JOF7040298
7. Dyer O. Covid-19: India sees record deaths as "black fungus" spreads fear. *BMJ*. 2021;373:n1238. doi:10.1136/BMJ.N1238
8. Essar MY, Khan H, Babar MS, et al. Mucormycosis, conflicts and COVID-19: A deadly recipe for the fragile health system of Afghanistan. *Int J Health Plann Manage*. 2021. doi:10.1002/HPM.3292
9. Hindustan Times. India reported over 45000 black fungus cases so far says mandaviya. https://www.indiatoday.in/india/story/over-45-000-cases-of-mucormycosis-reported-in-country-1830590-2021-07-21. Published 2021.
10. Sahoo JP, Panda B, Mishra AP, Samal KC. The Unseen "Fungal Infections" – An Extra Thrust Aggravating COVID Second Wave in India. *Biot Res Today*. 2021;3(5):354-356. https://bioticainternational.com/ojs/index.php/biorestoday/article/view/877. Accessed October 10, 2021.
11. Wattal C, Chakrabarti A, Oberoi JK, et al. Issues in antifungal stewardship: an opportunity that should not be lost. *J Antimicrob Chemother*. 2017;72(4):969-974. doi:10.1093/JAC/DKW506
12. Balarajan Y, Selvaraj S, Subramanian S V. Health care and equity in India. *Lancet*. 2011;377(9764):505. doi:10.1016/S0140-6736(10)61894-6
13. The Economic Times. black fungus: Make Mucormycosis a notifiable disease: Govt. https://economictimes.indiatimes.com/news/india/make-mucormycosis-a-notifiable-disease-govt/articleshow/82809062.cms. Published 2021. Accessed October 10, 2021.
14. Indian Council of Medical Research, New Delhi. Evidence Based Advisory in the Time of COVID-19 (Screening, Diagnosis & Management of Mucormycosis). https://www.icmr.gov.in/cmucormycosis.html. Published 2021. Accessed October 10, 2021.

15. Ministry of Health and Family Welfare. Government of India proactively makes all round efforts to ramp up supply and availability of Amphotericin-B anti-fungal drug for treatment of Black Fungus disease. https://pib.gov.in/PressReleasePage.aspx?PRID=1720563. Published 2021.
16. The Hindu BusinessLine. Govt restricts export of Amphotericin-B drug. https://www.thehindubusinessline.com/news/national/govt-restricts-export-of-amphotericin-b-drug/article34702010.ece. Published 2021. Accessed October 10, 2021.
17. Arun AB, Hasan MM, Rackimuthu S, Ullah I, Mir T, Saha A. Antifungal drug shortage in India amid an increase in invasive fungal functions during the coronavirus disease 2019 (COVID-19) pandemic. *Infect Control Hosp Epidemiol*. September 2021:1-2. doi:10.1017/ICE.2021.426
18. Hindustan Times. Black market for black fungus drugs: Nursing staff, medical reps arrested. https://www.hindustantimes.com/cities/others/black-market-for-black-fungus-drugs-nursing-staff-medical-reps-arrested-101623953780676.html. Published 2021. Accessed October 10, 2021.