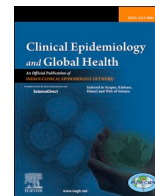




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From black to white: A roadmap to containing the rise of candidiasis amidst COVID-19 and mucormycosis in India

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ABSTRACT

With numbers of active COVID-19 cases in India falling in recent weeks and the healthcare system finally showing signs of coping with the mucormycosis epidemic, several new reports of COVID-19 cases linked to “white fungus” have emerged. This has led to rising concern with the potential to stretch the capacity of an already burdened healthcare system. Moreover, the implications of this disease in the COVID-19 population and its consequences on the health and socio-economic structure of the country have not been vastly studied. This commentary explores the need for government efforts in the context of containing candidiasis during the pandemic and provides key recommendations on combating this imminent public health challenge.

1. Introduction

A combination of potentially more transmissible and deadly mutant strains of SARS-CoV-2, scarcity of medical supplies, and superspreading events have all led to a potent resurgence of COVID-19 cases in India.^{1–3} On 6th May 2021, India witnessed a record-breaking peak of 414,000 new COVID-19 cases. This deadly second peak was accompanied with mucormycosis and aspergillosis infections in critically ill COVID-19 cases⁴ that were linked to alarmingly increasing rates of morbidity and mortality.⁵ About 71% of all documented mucormycosis case reports were reported in India,⁶ with the majority observed in the states of Gujarat, Maharashtra, and Bihar.⁷

Adding another dimension to the burden of the COVID-19 pandemic was the emergence of the ‘white fungus’ infection of which the first case had been traced to Bihar and Madhya Pradesh.^{8,9} White fungus, caused by candida species, is thought to be more catastrophic than mucormycosis. In addition to the respiratory tract, it has the propensity to spread

to the brain, digestive tract, kidneys, nail beds, and genitals.¹⁰ An unusual case of candida abscess in brain was also detected in a patient during the post-COVID-19 recovery phase.¹¹ Chowdhary et al. assessed the clinical outcomes of 15 critically ill COVID-19 patients and showed a high case fatality rate of up to 60% with *Candida auris* accounting for two thirds of the cases.¹² Moreover, there is a lack of research that explores this newly emerging risk. In this paper, we present a scientific perspective on the magnitude of the white fungus outbreak, its potential implications on the COVID-19 pandemic, and provide key recommendations on containing this imminent public health challenge.

2. Government efforts to curtail fungal outbreaks amidst the COVID-19 pandemic

The emergence of secondary fungal infections in COVID-19 recovered patients posed unforeseen challenges to the Indian health system amid the catastrophic second wave of COVID-19.¹³ On 21 May 2021,

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Union Health Ministry wrote letters to all the states and union territories to declare mucormycosis as a notifiable disease under Epidemic Disease Act 1897, thereby compelling all the government and private hospitals to report every suspected and confirmed case of mucormycosis to the Union Health Ministry.¹⁴ The government issued an advisory for healthcare bodies to ensure well-regulated use of steroids in the treatment of COVID - 19, and proper monitoring of glycemic index in diabetic patients. 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.^{15,16}

The rise in numbers of fungal infections resulted in a dramatic increased demand for the antifungal drug Amphotericin B leading to acute shortage and creating a black market for an already expensive drug.¹⁵ In addition, disrupted transportation affecting supply chains due to lockdowns and travel restrictions alongside significantly reduced import of active pharmaceutical ingredients (APIs) further worsened the shortage of essential drugs.¹⁷ To ensure the proper supply and availability of antifungal drugs, as per 'Whole of Government Approach',¹⁸ the Union Health Ministry along with the Department of Pharmaceuticals and the Ministry of External Affairs instructed domestic manufacturers to ramp up the production with a target of 163,752 vials of Amphotericin B in the month of May 2021, which was further expected to increase to 255,114 vials in June 2021. In addition to this, vials were imported from supporting foreign nations, thereby increasing the overall nationwide availability of Amphotericin B injections to 570,114 in June 20, 21.¹⁸ National pharmaceutical companies were expected to produce 111,000 vials per month cumulatively.¹⁸ To ensure the equitable distribution of drugs among healthcare organizations, the approach of 'Survey Based Allocations' on the basis of data collected from individual states and union territories was implemented.¹⁹

Even though India has been lauded by prominent organizations around the world for its vaccination efforts against COVID-19, there still remains room for improvement as vaccination plans are still inadequate and not agreeably equitable.²⁰ The government of India under "Mission COVID Suraksha" has also promoted public-private partnership to channelize vaccine manufacturing companies to increase vaccine production in order to meet the increasing demand, thus protecting the population from COVID-19 and secondary fungal infections.²¹

3. Potential implications

The potential implications due to failure to contain the candidiasis outbreak can be devastating for the medical, social and economic situation of the country. This intensity of COVID-19 and mucormycosis complications coupled with the rise in candidiasis may cause a significant burden on the Indian healthcare system. This could negatively impact the physical and psychological state of healthcare workers resulting in suboptimal patient care, further limiting the resources available to treat and prevent other existing diseases. The paradigm shift of COVID-19 related complications has also created a pathological window for opportunistic fungal outbreaks, such as the rise of 'Yellow Fungus' (*Mucor Septicus*).²² This further stagnates the development of future public health, treatment and research in the field.

Failure to contain the rise in COVID-19 related candidiasis further hamper recovery from the current cycle of repeated national lockdowns, travel restrictions, loss of normalcy and the associated bio-socio-economic crisis that has characterized the COVID-19 pandemic.

4. Recommendations

A multi-modal targeted approach involving all relevant stakeholders as well as that of the general population is necessary to tackle the challenges posed by COVID-19 related mucormycosis and candidiasis. Enhancing epidemiological surveillance across all health centers and hospitals across India is extremely vital for early detection of future fungal outbreaks. Setting up of a national coordinated centralized

system or database consisting of information on all diagnosed cases of invasive fungal infections along with other relevant clinical and demographic details can also aid in reallocating resources such as funds, drugs and other medical resources to regions with increased incidence and prevalence of fungal infections. This would also help governmental authorities and medical administrations in mobilizing essential first line drugs for treatment such as Amphotericin B which is currently a sparse commodity. Steps taken to ramp up the production of antifungal medication whilst effectively limiting the cost of the same, would also greatly reduce the expenses spent in procurement of the necessary drugs amidst the COVID-19 pandemic.²³

Patients must exercise extreme caution by following public health guidelines for invasive fungal infections during the pandemic. Awareness campaigns among the general population are needed to highlight the symptoms and signs of these invasive fungal infections, thereby increasing the chances of early intervention and favorable treatment outcomes.¹⁸

Reinforcing the need to adhere to sterile precautions and practices especially in the context of healthcare settings can help reduce the number of cases of candidemia caused by *C. auris*. Similarly, adopting measures such as 1) wearing facemasks whilst visiting construction sites; 2) wearing boots, full trousers, long sleeved shirts, and gloves while handling soil, moss, or manure; and 3) maintaining personal hygiene can collectively aid in preventing mucormycosis infection.

5. Conclusion

With a high fatality rate, the 'white fungus' has emerged amidst India's rising mucormycosis cases during the COVID-19 pandemic. At this juncture, an additional invasive fungus can cause potential harm to the healthcare system. To prevent a possible surge in candidiasis, the Indian government must take lessons from the mucormycosis experience and strengthen their response to efficiently mitigate this imminent public health challenge.

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