



**ORIGINAL RESEARCH PAPER**

**Pharmacology**

**EVALUATION OF PRESCRIBING PATTERN OF ANTIFUNGAL DRUGS AND CLINICAL OUTCOME IN POST-COVID SUSPECTED CASES OF MUCORMYCOSIS AT DEDICATED COVID HOSPITAL: AN OBSERVATIONAL STUDY.**

**KEY WORDS:** Covid-19, mucormycosis, antifungal, amphotericin B.

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**ABSTRACT**

**INTRODUCTION:** Threat of COVID-19 pandemic is still not over and another threat of Post-COVID mucormycosis has started looming over the horizon. Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment are important for improving outcomes for patients with mucormycosis. The present study was done to evaluate the prescribing pattern of antifungal drugs and clinical outcome in Post-covid suspected cases of Mucormycosis at Dedicated COVID hospital. **MATERIALS AND METHODS:** The present observational study was done after obtaining the Ethics committee approval from Institutional Ethics Committee (IEC), Government Medical College, Jalgaon. We collected the data of previous treatment records, demographics, comorbidities, laboratory investigations and clinical outcome from the case files of patients admitted with diagnosis of clinically suspected mucormycosis with history of COVID19 infection. **RESULTS:** Out of the total 112 patient records, majority belonged to age group 51-60 years comprising of 37 patients (33%). In the present study, Amphotericin B was most commonly prescribed antifungal drug followed by posaconazole, fluconazole and itraconazole. Amongst Amphotericin B, lipid emulsion was most commonly prescribed in 82 patients (73.2%), followed by liposomal formulation in 58 patients (51.8%). **CONCLUSION:** The present study aims to provide data on prescribing trends of antifungal drugs in post-COVID clinically suspected cases of mucormycosis, which is lacking in published Indian literature.

**INTRODUCTION:**

Threat of COVID-19 pandemic is still not over and another threat of Post-COVID mucormycosis has started looming over the horizon. The country has recorded 11,717 cases of "Black Fungus" or Mucormycosis with Maharashtra reporting 2,770 cases and Gujarat 2,859 cases.<sup>1</sup>

Mucormycosis (previously called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These molds live throughout the environment. Mucormycosis mainly affects people who have health problems or take medicines that lower the body's ability to fight germs and sickness. It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury.<sup>2</sup>

Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide, in particular from India. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.<sup>3</sup>

Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment are important for improving outcomes for patients with mucormycosis. Amphotericin B, posaconazole, and isavuconazole are active against most mucormycetes. Lipid formulations of amphotericin B are often

used as first-line treatment. Medications active against Aspergillus such as voriconazole are not active against mucormycetes, and there is some evidence to suggest that pre-exposure to voriconazole may be associated with increased incidence of mucormycosis in some patients. In addition, surgical debridement or resection of infected tissue is often necessary, particularly for rhinocerebral, cutaneous, and gastrointestinal infections. Control of the underlying immunocompromising condition should be attempted when possible. The efficacy of other treatments such as hyperbaric oxygen therapy is uncertain but have been useful in certain situations.<sup>2,4</sup>

After exhaustive literature search we could not find much published data on prescribing pattern of antifungal drugs in post covid suspected patients of mucormycosis. Hence the present study was done to evaluate the prescribing pattern of antifungal drugs and clinical outcome in Post-covid suspected cases of Mucormycosis at Dedicated COVID hospital.

**MATERIALS AND METHODS:**

The present observational study was done after obtaining the Ethics committee approval from Institutional Ethics Committee (IEC), Government Medical College, Jalgaon. We collected the data of previous treatment records, demographics, comorbidities, laboratory investigations, prescription of antifungal drugs and clinical outcome from the case files of patients admitted with diagnosis of clinically suspected mucormycosis with history of COVID19 infection. These case files were obtained from medical record section of Government Medical College, Jalgaon after taking required permission. After going through all the records, the required data was entered in Microsoft Excel sheet. For demographic characteristics, descriptive statistics were used. All the data was represented in the form of percentage.

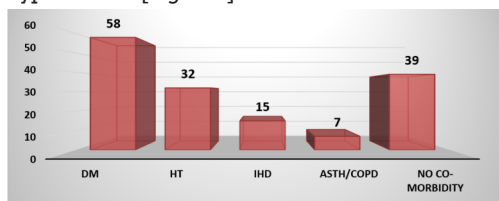
**RESULTS:**

Out of the total 112 patient records, majority belonged to age group 51-60 years comprising of 37 patients (33%), followed by 32 patients (29%) in the age group 41-50 years age group. On gender analysis, most of the patients were males comprising of 70 patients (64%), while 42 patients (37%) were females [Table 1].

**Table 1: Demographic details of the patients in the present study.**

Sr. No.	Category	Sub-category	n (%)
1	Age	Upto 30	8 (7%)
		31-40	10 (9%)
		41-50	32 (29%)
		51-60	37 (33%)
		61-70	18 (16%)
		above 71	7 (6%)
2	Gender	Male	70 (63%)
		Female	42 (37%)

On analyzing the co-morbidities, it was found that most common co-morbidity was diabetes mellitus seen in 58 patients (52%), followed by 32 patients (28.5%) suffering from hypertension [Figure 1].



**Figure 1: Co-morbidities in patients of the present study.**

In the present study, Amphotericin B was most commonly prescribed antifungal drug followed by posaconazole, fluconazole and itraconazole. Amongst Amphotericin B, lipid emulsion was most commonly prescribed in 82 patients (73.2%), followed by liposomal formulation in 58 patients (51.8%), plain formulation in 27 patients (24%) and lipid complex in 23 patients (20.5%) [table 2].

**Table 2: Prescribing trend of antifungal drugs in the present study.**

Sr. No.	Prescribed antifungal drugs	Types	No. of Patients	Percentage
1	Amphotericin B	Plain	27	24.1
		Liposomal	58	51.8
		Emulsion	82	73.2
		Lipid Complex	23	20.5
2	Posaconazole		39	34.8
3	Fluconazole		23	20.5
4	Itraconazole		18	16.1

The most commonly co-prescribed drugs along with antifungal drugs were antibiotics, of which fixed dose combination of piperacillin + tazobactam was most commonly prescribed in 102 patients (92%), followed by cefoperazone in 76 patients (67.9%). Vitamins were prescribed in all the patients, whereas insulin was given in 65 patients (58%). Heparin was co-prescribed in 39 patients (34.8%) [table 3].

**Table 3: Drugs co-prescribed with antifungal drugs in the present study.**

Sr. No.	Other co-prescribed drugs	No. of Patients	Percentage
1	Antibiotic	Cefoperazone	76 67.9
		Piperacillin+tazobactam	103 92.0
		Metronidazole	9 8.0
		Moxifloxacin	15 13.4
		Meropenam	25 22.3
		Linezolid	5 4.5

2	Vitamins	112	100.0
3	Insulin	65	58.0
4	Heparin	39	34.8
5	Amlodipine	21	18.8
6	Atorvastatin	13	11.6
7	Deriphyllin	8	7.1

**DISCUSSION:**

The pandemic coronavirus disease 2019 (COVID-19) continues to be a significant problem worldwide. While several treatment options have been evaluated, none except systemic glucocorticoids have been shown to improve survival in COVID-19. Unfortunately, the widespread use of glucocorticoids can lead to secondary bacterial or fungal infections. Invasive pulmonary aspergillosis complicating the course of COVID-19 is widely recognized<sup>5</sup>; however, mucormycosis is uncommonly suspected or diagnosed. Although amphotericin B, posaconazole, etc. are indicated for treatment of invasive fungal infections; data of prescribing pattern of antifungal drugs in post-COVID clinically suspected cases of mucormycosis in India is very scarce.

The most common age group affected in the present study was adult age group, which is in accordance with study done by Patel et al.<sup>6</sup> Most common patients in the present study were males, which was in corroboration with other such study.<sup>6</sup> Most common co-morbidity in the patients of present study was diabetes mellitus, followed by hypertension, ischemic heart disease. Similar findings were reported in other such study wherein DM was found as a predisposing factor in almost 88% of the patients of mucormycosis.<sup>6,7</sup>

Most commonly prescribed antifungal drug in the present study was amphotericin B. Lipid emulsion formulation was most commonly prescribed followed by liposomal, plain conventional and lipid complex formulations. Conventional amphotericin B has many challenges, both in terms of efficacy as well as safety. It has been found in various clinical trials in invasive fungal infections, that efficacy of liposomal and lipid formulations of amphotericin B is higher as compared to conventional one.<sup>8-11</sup> In terms of safety, conventional amphotericin is associated with more occurrence of infusion related reactions and nephrotoxicity. Liposomal amphotericin B negates these adverse events resulting in lesser occurrence of infusion reactions and nephrotoxicity. However, high cost is one of the major challenge with the use of liposomal preparation.<sup>7</sup> Apart from this, other antifungal drugs like posaconazole, fluconazole, itraconazole were also prescribed to the patients of present study. Similar trend was noted in a study done by Patel et al.<sup>6</sup>

In the present study antibiotics like cefoperazone and piperacillin + tazobactam were most commonly co-prescribed drugs along with multi vitamins. A significant number of patients with COVID-19 infection need extended hospital stay, owing to which they are at augmented risk of contracting nosocomial infections which predominantly include bacterial and fungal infections. Compromised capacity to remove bacteria and fungi due to release of various interleukins<sup>6,10</sup>; attenuated function of natural killer cells, macrophages, T cells and lately virus mediated mechanisms are some of the factors which are implicated in these secondary infections.<sup>14,15</sup> In a study done by Vijay S et al. on secondary infections in COVID patients in India, it was found that most commonly prescribed antibiotic was piperacillin + tazobactam and cefoperazone, which is in line with findings of the present study.<sup>16</sup>

In the present study insulin was prescribed in 58% of the patients. It is now well established that hyperglycemia can occur in patients of COVID-19 who are hospitalized, irrespective of previous blood sugar control or diagnosed case of diabetes mellitus.<sup>17,18</sup> Hyperglycemia is currently considered as a marker for poor prognosis in patients of COVID-19 and the risk of multiple organ failure, need for ventilation support, admission to ICU is increased in such

patients.<sup>19</sup> Thus, tight control of blood glucose in such patients is currently warranted.

Heparin was co-prescribed in 35% of the patients in the presents study. Recent literature regarding COVID-19 has warned us regarding increased occurrence of thrombo-embolic episodes in these patients.<sup>20</sup> Inflated inflammatory events causing clotting activation and injury to endothelium ultimately leading to hypercoagulable state are some of the postulations cited for the occurrence of thrombo-embolic episodes.<sup>21,22</sup>

As per latest Indian guidelines, unfractionated or low molecular weight heparin is indicated in treatment of moderate to severe cases of COVID 19 admitted to ward.<sup>23</sup>

The present study was not without limitations. The prescription trends of antifungal drugs were not analyzed in correlation with outcomes in post-COVID clinically suspected cases of mucormycosis. Secondly, clinically suspected cases of mucormycosis were involved and not the mycological confirmed ones. However, the findings of the present study will give a picture about prescribing patterns of antifungal drugs and other co-prescribed drugs in treatment of post-COVID mucormycosis.

**CONCLUSION:**

In the present study, lipid emulsion followed by liposomal amphotericin B was most commonly prescribed antifungal drug. Most common co-prescribed antibiotic was fixed dose combination of piperacillin + tazobactam followed by cefoperazone. Apart from these insulin, heparin and multivitamins were also frequently co-prescribed. The present study aims to provide data on prescribing trends of antifungal drugs in post-COVID clinically suspected cases of mucormycosis, which is lacking in published Indian literature.

**Conflicts of interest:** None.

**Source of funding:** None.

**Ethics approval:** Taken prior to the start of the study.

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