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Original Research Article

Clinical outcome and toxicity in post-COVID suspected cases of mucormycosis treated with amphotericin B at dedicated COVID hospital: a prospective observational study

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ABSTRACT

Background: Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported world-wide, in particular from India. Lipid formulations of amphotericin B are often used as first-line treatment. Present study aims to assess and analyze clinical outcome and toxicity in post-COVID suspected cases of mucormycosis treated with amphotericin B at dedicated COVID hospital.

Methods: The present study was a prospective observational study conducted at government medical college, Jalgaon which was a dedicated COVID hospital. Clinically suspected cases of mucormycosis treated with Amphotericin B were included in the study. 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 COVID-19 infection.

Results: Out of 57 patients, majority of them belonged to age group of 51-60 years comprising of 21 patients (37%) and 86% had involvement of one or more paranasal sinus/es. On analyzing prescription pattern and outcomes in patients of present study, it was found that majority of the patients had recovered completely comprising of 40 patients (70%), of which 21 patients (37%) had received liposomal amphotericin B, followed by lipid emulsion amphotericin B in 12 patients (21%).

Conclusions: The present study was first of its kind to analyze the prescribing trend of amphotericin B and outcomes in clinically suspected post-COVID cases of mucormycosis. Liposomal amphotericin B was found to be more effective and safer in terms of better recovery rate and less adverse events.

Keywords: COVID-19, Mucormycosis, Liposomal, Amphotericin B, Outcome

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.¹

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.²

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.³

Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment is 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 rhino cerebral, cutaneous, and gastrointestinal infections. Control of the underlying immunocompromising condition should be at possible. The efficacy of other treatments such as hyperbaric oxygen therapy is uncertain but have been useful in certain situations.^{2,4}

Amphotericin B has emerged as drug of choice for the treatment of mucormycosis, especially in cases of rhino cerebral mucormycosis. Mainly 3 types of amphotericin B preparations are available for clinical use- conventional Amphotericin B, Lipid Emulsion formulation and liposomal preparation. All preparations of amphotericin B are known to cause post infusion reactions in patients and amphotericin B is regarded as highly nephrotoxic drug.⁴ Literature is lacking in data about clinical outcome of mucormycosis cases treated with amphotericin B, furthermore literature is also lacking in data about effect of amphotericin B on kidney function test in post COVID suspected cases of mucormycosis. Present study aims to assess and analyze clinical outcome and toxicity in post-covid suspected cases of mucormycosis treated with Amphotericin B at Dedicated COVID hospital.

METHODS

The present study was a prospective observational study conducted at government medical college, Jalgaon which was a dedicated COVID hospital. Clinically suspected cases of mucormycosis treated with amphotericin B were included in the study. 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 COVID-19

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 data was entered in the Microsoft excel sheet. Data was analyzed with the help of Microsoft excel. For demographic characteristics and clinical outcome descriptive statistics were used. The study was done after obtaining the institutional ethics committee approval. Nephrotoxicity was considered as deranged values of serum creatinine and, or blood urea nitrogen.

RESULTS

Out of 57 patients, majority of them belonged to age group of 51-60 years comprising of 21 patients (37%), followed by 19 patients (33%) in age group 41-50 years. On gender analysis, majority of the patients were males i.e., 33 patients (58%) as compared to 24 females (42%). Most of the patients were residing in rural area which comprised of 34 patients (60%) (Table 1).

Table 1: Socio-demographic details of patients in the present study.

Category	Sub-category	Number of patients (%)
Age group (Years)	21-30	5 (8.7)
	31-40	5 (8.7)
	41-50	19 (33)
	51-60	21 (37)
	>60	7 (12)
Gender	Male	33 (58)
	Female	24 (42)
Residence	Urban	23 (40)
	Rural	34 (60)

Majority of the patients had involvement of one or more paranasal sinus/es. These comprised of 86% of the total patients. Paranasal sinus and eye were involved in 12% of the patients, while paranasal sinus and oral cavity involvement was seen in 2% of the patients (Figure 1).

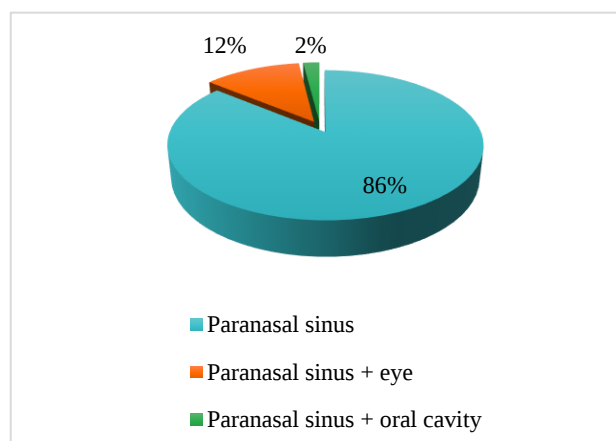


Figure 1: Percentage of patients of sinus, eye and oral cavity involvement by mucormycosis.

Of all the known risk factors for mucormycosis in post-COVID patients, history of steroid use was most common risk factor in 46 patients (81%), followed by history of oxygen supplementation during COVID treatment in 31 patients (54%). The 19 patients (33%) required admission to intensive care unit (ICU), while 11 patients (19%) required ventilatory support. Amongst the patients who required oxygen supplementation, majority of the patients required oxygen therapy for 5-10 days (24 patients, 42%). The patients who required steroids during COVID treatment, majority of them received steroids for 11-15 days (46%), followed by 5-10 days (35%) (Table 2).

Table 2: Risk factors associated with mucormycosis in post-COVID patients in the present study.

Risk factor for mucormycosis (during COVID infection)	Category, n (%)	Sub-category	N (%)
Oxygen supplementation (Days)	Yes, 31 (54)	<5	4 (7)
		5-10	24 (42)
		11-20	2 (3.5)
		>20	1 (1.7)
	No		26 (46)
ICU admission (Days)	Yes, 19 (33)	<5	3 (5)
		5-10	8 (14)
		>10	8 (14)
	No		38 (67)
Ventilator required (Days)	Yes, 11 (19)	<5	4 (7)
		>5	7 (12)
	No		46 (81)
Steroid required (Days)	Yes, 46 (81)	<5	4 (7)
		5-10	20 (35)
		11-15	26 (46)
		16-20	7 (12)
	No		11 (19)

In the present study, all the patients received medical treatment, of which 7 patients additionally received surgical treatment as well (Figure 2).

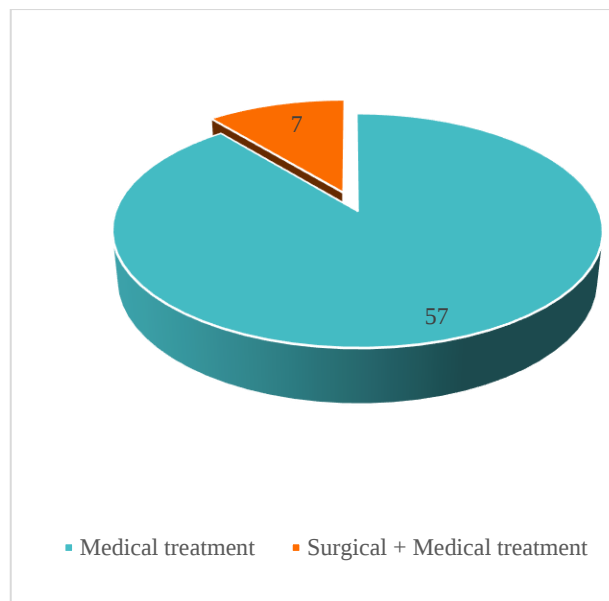


Figure 2: Treatment received by patients of suspected mucormycosis in the present study.

On analyzing prescription pattern and outcomes in patients of present study, it was found that majority of the patients had recovered completely comprising of 40 patients (70%), of which 21 patients (37%) had received liposomal amphotericin B, followed by lipid emulsion amphotericin B in 12 patients (21%). The 12 patients (21%) were transferred to other hospital, of which 5 patients (8.7%) had received lipid emulsion amphotericin B, followed by liposomal amphotericin B in 3 patients (5%). Five patients died during the course of treatment, of which 2 patients had received plain amphotericin B, liposomal amphotericin B was not given to any of these patients. Three patients received liposomal amphotericin B and posaconazole, of which 2 patients showed complete recovery and 1 patient was transferred to other hospital. Complete recovery was seen more in patients who had received liposomal amphotericin B ($p=0.03$) (Table 3).

Table 3: Analysis of antifungal drugs prescribed and outcomes in patients of suspected mucormycosis in present study.

Antifungal therapy given	Outcomes, n (%)			Total (%)
	Recovered	Transfer to other hospital	Death	
Plain amphotericin B	2 (3)	1 (1.7)	2 (3)	5 (8.7)
Liposomal amphotericin B	21 (37)	3 (5)	1 (1.7)	25 (44)
Lipid complex amphotericin B	3 (5)	2 (3)	1 (1.7)	6 (10.5)
Lipid emulsion amphotericin B	12 (21)	5 (8.7)	1 (1.7)	18 (31.5)
Liposomal amphotericin B + posaconazole	2 (3)	1 (1.7)	0	3 (5)
Total	40 (70)	12 (21)	5 (8.7)	57 (100)
P value	0.03	>0.05	>0.05	

Total 22 adverse events were encountered in the patients of present study, of which most common adverse effect was infusion reaction, which was seen in 14 patients (24%) and nephrotoxicity was seen in 8 patients (14%). All the patients who received plain amphotericin B encountered infusion reaction and nephrotoxicity. These reactions were least in patients who had received liposomal amphotericin B (Table 4).

Table 4: Adverse effects encountered in patients who received amphotericin B.

Type of amphotericin B	Adverse effect of amphotericin B, n (%)		Total
	Infusion reaction	Nephrotoxicity	
Plain	5 (9)	5 (9)	22
Liposomal	1 (1.7)	0	
Lipid complex	5 (8.7)	2 (3.5)	
Lipid emulsion	3 (5.2)	1 (1.7)	
Total	14 (24)	8 (14)	

DISCUSSION

COVID-19 associated mucormycosis has been increasingly seen in second wave of COVID-19 pandemic in India. *Mucor* *Mucorales* has been implicated as the most common cause of mucormycosis in such cases. Such type of mucormycosis is most commonly seen in patients with immunosuppressed status, presence of one or more co-morbidities like diabetes, kidney disease, indiscriminate use of corticosteroids.⁵ Amphotericin B is most commonly prescribed drug in such scenario, however there is paucity of data related to its effect on outcomes in patients of post-COVID mucormycosis.⁶ Therefore, the present study was planned to assess the outcomes in patients of post-COVID mucormycosis who had received amphotericin B.

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.⁷ Most common patients in the present study were males, which was in corroboration with other such study.⁷ Most common predisposing factor in the present study was steroid use (81%), followed by oxygen supplementation (54%), admission to ICU (33%), ventilator support (19%). Out of these, majority of the patients had received prolonged oxygen supplementation and ventilator support. Improper sanitization of oxygen cylinders, disposable humidifiers and most importantly use of impure tap water in oxygen humidifiers and oxygen concentrators have been implicated reasons for these risk factors.⁸ Long term steroid use in high dose has been implicated as a major contributory factor in increased incidence of mucormycosis infection in post-COVID cases.⁸

In the present study majority of the patients had involvement of one or more paranasal sinus/es. These comprised of 86% of the total patients. Paranasal sinus and

eye were involved in 12% of the patients, while paranasal sinus and oral cavity involvement was seen in 2% of the patients. Similar findings were seen in a study done Sharma et al wherein most common involvement was seen with sinus followed by sinus with eyes and sinus with oral cavity.⁹

The survival and outcome rate in patients of mucormycosis have been found to be higher in patients who been treated with combined approach of surgical and medical therapy. Surprisingly, in the present study majority of the patients were treated with medical therapy and only 12% of the patients were treated with medical with surgical therapies. This is in contrast with findings of a multi-centric study wherein almost 62% of the patients of mucormycosis were treated with combined approach.⁷ The most probable reason for such discrepant findings might be the inclusion of clinically suspected cases of mucormycosis in the present study, whereas the multi-centric study included confirmed cases of mucormycosis.

In the present study, majority of the patients had received liposomal amphotericin B which was in corroboration with other study findings.⁷ Out of total number of patients who recovered completely majority had received liposomal amphotericin B, followed by lipid emulsion amphotericin B in 12 patients. This might be attributed to multiple advantages offered by liposomal formulation of amphotericin B like, milder infusion reactions, lower nephrotoxicity, target specific delivery. Also, it was found that efficacy of liposomal amphotericin B was higher as compared to conventional amphotericin B.¹⁰

Mortality was encountered in 8.7% of the patients. Out of which majority of the patients had received the conventional amphotericin B formulation. Similar findings were noted in a study done by Patel et al wherein a multivariate analysis revealed that treatment with conventional amphotericin B, rhino-orbital mucormycosis with cerebral extension were implicated as major risk factors for increased mortality.⁷ There was no death in patients who had received liposomal amphotericin B.

In the present study, adverse events in the form of infusion reaction were seen in 14 patients (24%) and nephrotoxicity was seen in 8 patients (14%). Overall, the adverse events were least in patients who had received liposomal amphotericin B. After exhaustive literature search, we could not find studies to analyze the incidence of adverse events associated with the use of amphotericin B in patients of post-COVID mucormycosis.

Limitations

The present study was not without any limitations. The study included clinically suspected cases of mucormycosis and the sample size was small. It is recommended that such study should be carried out as a multicentric design with inclusion of confirmed cases of mucormycosis.

CONCLUSION

The present study was first of its kind to analyze the prescribing trend of amphotericin B and outcomes in clinically suspected post-COVID cases of mucormycosis. Liposomal amphotericin B was found to be more effective and safer in terms of better recovery rate and less adverse events. However, more such multicentric studies are warranted to compare and generalize the findings of the present study.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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