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An Evaluation of Risk Factors and Pharmacotherapy in Post SARS-CoV-2 (COVID-19) Rhino-Cerebral Mucormycosis Patients in a Tertiary Care Teaching Hospital in Ahmedabad

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ABSTRACT

Introduction: *Mucormycosis is a highly aggressive fungal infection with 0.14 cases/1000 population prevalence in India. There have been case reports of post-COVID-19 mucormycosis but the relationship is still unclear.* ***Objectives:*** *This study was done to identify possible risk factors and to evaluate prescribing patterns of anti-fungal agents and associated adverse drug reactions in post-COVID-19 mucormycosis patients in tertiary care hospitals in Ahmedabad.* ***Methods:*** *In this prospective, observational study, patients of post-COVID-19 rhino-cerebral mucormycosis were enrolled and history-based identification of possible risk factors was done over a period of 3 months. The prescribing pattern of anti-fungal agents and supportive treatment were evaluated according to WHO core prescribing indicators. Common ADRs were recognized and their causality was established.* ***Results:*** *Out of 68 enrolled patients, 61 were COVID-19 positive. 43 had mucormycosis with orbital extension and 18 had mucormycosis without orbital extension. 66.7% of patients had a history of hospitalization, 50% of patients received oxygen therapy, 61.1% patients had a history of diabetes mellitus type-2, and 66.7% patients received treatment with glucocorticoids. All patients received antibiotics, 77.8% of patients had a history of steam inhalation during COVID-19 illness. Amphotericin-B 50 mg/kg was given to 52 patients for 14 days. The average number of medicines/encounters was 9.1 and 17.6. The percentage of encounters containing antimicrobials and injections was 100%.* ***Conclusion:*** *It was observed in the present study that patients who had a history of hospitalization, oxygen therapy, diabetes mellitus and steam inhalation had a high risk of post-COVID rhino-cerebral mucormycosis. Polypharmacy was observed. The highest incidence of ADR observed during the use of antifungal agents was hypokalemiao.*

Keywords: Mucormycosis, Amphotericin B, Pharmacotherapy, COVID-19

Abbreviations: RT-PCR: Reverse Transcription-Polymerase Chain Reaction, MRI: Magnetic Resonance Imaging, CT: Computed Tomography, AIDS: Acquired Immune Deficiency Syndrome, ADR: Adverse Drug Reaction, CNS: Central Nervous System, WHO-UMC: World Health Organization-Uppsala Monitoring Center

INTRODUCTION

Mucormycosis is a highly aggressive fungal infection caused by members of the order Mucorales which are ubiquitous. The most common types that cause mucormycosis are *Rhizopus* species and *Mucor* species. *Rhizomucor* species, *Syncephalastrum* species, *Cunninghamella bertholletie*, *Apophysomyces*, *Lichtheimia* (formerly *Absidia*), *Saksenaea*, and *Rhizomucor* are other examples [1].

The prevalence of mucormycosis in India is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population [2].

It occurs in hosts with immune or metabolic impairment. The risk factors identified are Diabetes mellitus, particularly with ketoacidosis, treatment with glucocorticoids, hematologic malignancies, hematopoietic cell transplantation,

solid organ transplantation, treatment with desferoxamine, iron overload, AIDS, Injection drug use, trauma/burns, malnutrition [3].

Aspergillosis and Candidosis remain the most prevalent opportunistic infections in such patients, but diseases caused by zygomycetes have become of increasing importance. Treatment or prophylaxis with voriconazole, itraconazole or caspofungin seems to be associated with the development of zygomycosis. More intensive chemotherapy and immunosuppression, combined with exposure to antimycotic drugs that are not active against zygomycetes, may be new risk factors [4]. There have been case reports of mucormycosis in patients diagnosed with Coronavirus Disease 2019 (COVID-19), but the relationship between these two infections is unclear. Some of the infections of mucormycosis were diagnosed several days to a couple of weeks after being admitted for COVID- 19, and it seems reasonable to assume that the mucormycosis (rhinocerebral and pulmonary in these cases) was a secondary infection arising in a critically-ill patient on steroids [3].

Patients with diabetes mellitus usually develop Rhino-Orbital-Cerebral Mucormycosis (ROCM), patients with haematological neoplasms tend to develop the sino-pulmonary disease, and trauma patients present with necrotizing skin and soft tissue infections. Thus, in India, sinus disease predominates and the CNS is the third most common site of infection after the paranasal sinuses and orbit [5].

The diagnosis of mucormycosis relies upon the identification of organisms in tissue by histopathology with culture confirmation [6].

Amphotericin B (AMB) (including lipid formulations) is considered the drug of choice for the primary treatment of mucormycosis. Other available antifungal agents prescribed are triazole Posaconazole and Isavuconazole. Echinocandins demonstrate modest activity when administered with lipid Amphotericin B formulation. Surgical debridement can also be done according to CT imaging. There is no standard duration of treatment for mucormycosis. Continuation is according to a principle that antifungal therapy of mucormycosis is continued until resolution of all clinical, laboratory, and imaging signs and symptoms of infection and reversal of immunosuppression [7].

MATERIALS AND METHODS

This prospective, observational study was conducted in mucor wards of the civil hospital which is a tertiary care teaching hospital situated in Ahmedabad, Gujarat over a period of 3 months.

The objectives of the study were to identify possible risk factors and to evaluate prescribing patterns in patients of post-COVID-19 mucormycosis patients. The secondary objective was to observe adverse drug reactions of antifungal agents prescribed.

After taking approval from the Institutional Ethics Committee of civil hospital, Ahmedabad, patients who were tested positive for COVID-19 by RT-PCR SARS-COV-2 and later developed rhino-cerebral mucormycosis, who were more than 18 years of age and willing to give written informed consent were included. Patients on immunosuppressant agents and having malignancy were excluded from the study.

Demographic details and provisional diagnosis based on biopsy as well as MRI and CT scan of paranasal sinuses and brain were recorded in pre-tested case record form. History-based identification of possible risk factors of post-COVID-19 mucormycosis was done. Pharmacotherapy of mucormycosis was evaluated according to WHO core prescribing indicators. Adverse drug reactions observed were evaluated according to the WHO-UMC scale.

RESULTS

For the convenience of analysis, patients were divided into two groups i.e. patients having mucormycosis with orbital extension and mucormycosis without orbital extension. A total of 68 patients with mucormycosis were enrolled. But among these 61 were patients with COVID-19 positive test. 43 patients were diagnosed to have mucormycosis with orbital extension and 18 patients had mucormycosis without orbital extension.

Evaluation of Possible Risk Factors

Out of 61 patients with mucormycosis 66.7% of patients had a history of hospitalization, 50% of patients received oxygen therapy, 61.1% patients had a history of diabetes mellitus type-2, and 66.7% and 33.3% patients received

treatment with glucocorticoids and remdesivir respectively. 100% of patients received antibiotics and supplements such as vitamins and zinc, 77.8% of patients had a history of steam inhalation during their COVID-19 illness.

Table 1 and Figure 1 depict the possible risk factors among post-COVID-19 patients.

Table 1 Possible risk factors of mucormycosis (n=61)

Possible Risk factors	No. of patients (n=61)	Percentage (%)
Hospitalization	37	66.7
Oxygen therapy	30	50
ICU stay	1	0
Diabetes mellitus type 2	33	61.1
Diabetes mellitus type 1	3	0
Hypertension	15	27.8
Hypertension+Diabetes mellitus type 2	11	22.2
Treatment with glucocorticoids	36	66.7
Treatment with Remdesivir	17	33.3
Treatment with tocilizumab	0	0
Treatment with antibiotics	61	100
Treatment with supplements	61	100
Treatment with ivermectin	1	0
Steam inhalation	49	77.8
Wearing same mask	0	0

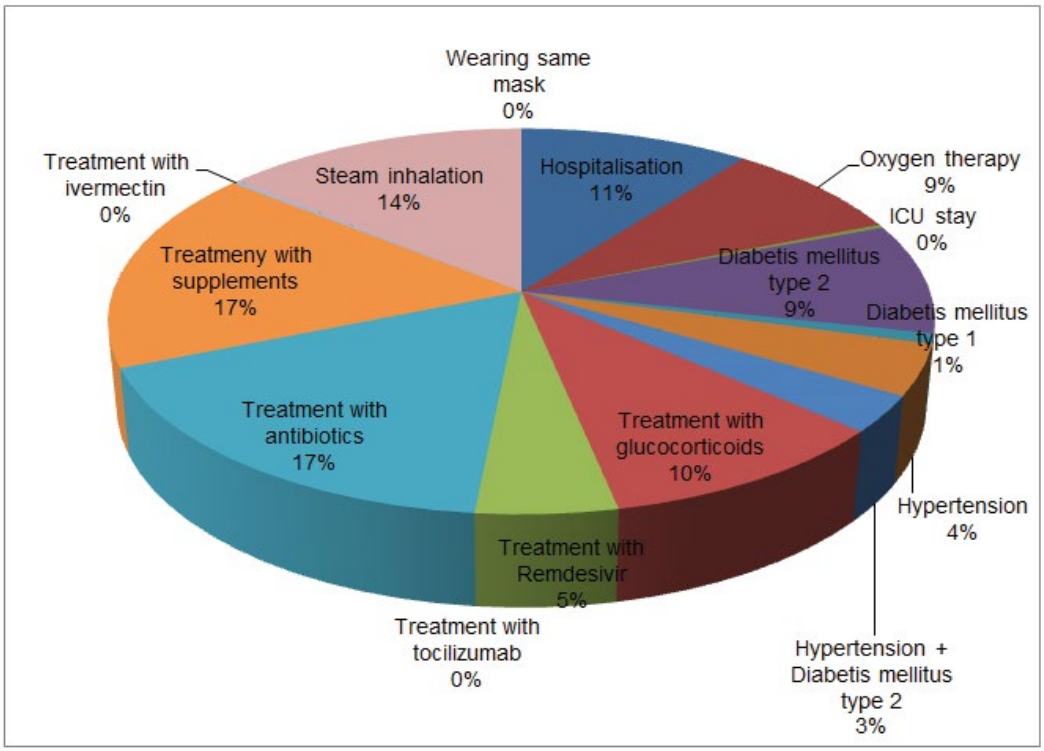

Figure 1 Overall distribution of possible risk factors

Among patients of mucormycosis with orbital extension (n=43), 29 patients received oxygen therapy with different modes of ventilation (Figure 2).

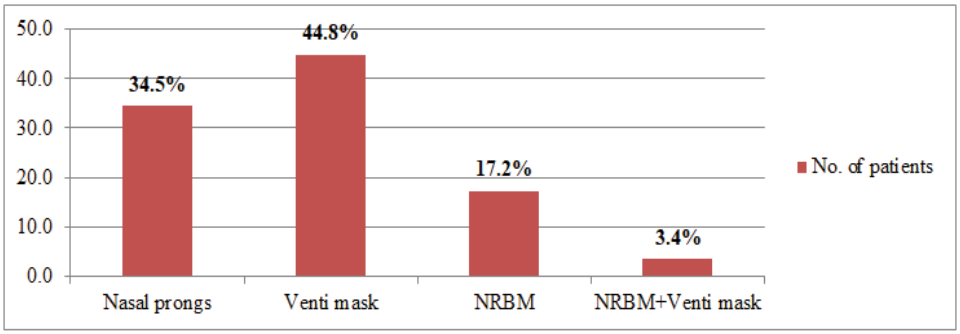

Figure 2 Modes of oxygen therapy among patients of mucormycosis with orbital extension patients (n=29) (NRBM: Non-Re-Breather Mask)

Out of 36 patients who had received corticosteroids during COVID- 19 illness, 15 had been given dexamethasone, 16 had been given prednisolone while the history of 5 patients was not known.

Evaluation of Pharmacotherapy

Among patients of mucormycosis without orbital extension 164 medicines were prescribed of which 110 were prescribed by generic name and 54 were prescribed by brand name. Among patients of mucormycosis with orbital extension 755 medicines were prescribed which 500 were prescribed by generic name and 204 were prescribed by brand name (Table 2).

Table 2 Evaluation of pharmacotherapy according to WHO core prescribing indicators (n=61)

WHO core indicators	Mucormycosis without orbital extension (n=18)	Mucormycosis with orbital extension (n=43)
Average number of medicines/encounter	9.1	17.6
Percentage of encounter with antibiotics	100%	100%
Percentage of encounter with injections	100%	100%
Percentage of drugs prescribed by generic name	67.10%	72.90%
Percentage of drugs prescribed from essential medicine list	91%	90.10%

All 61 patients received anti-fungal agents. 52 patients received conventional Amphotericin B, 4 patients received liposomal amphotericin B, 5 patients received both and 7 patients also received posaconazole (Figure 3).

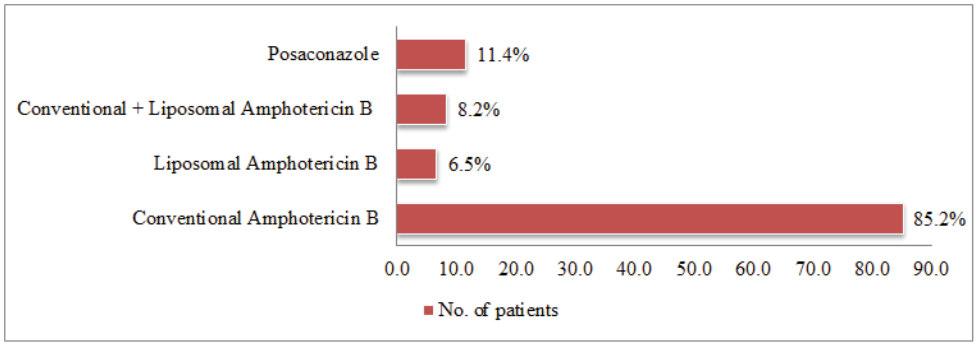

Figure 3 Anti-fungal agents prescribed (n=61)

Evaluation of Adverse Drug Reactions

Total 203 adverse drug reactions were observed during this study period (Table 3).

Table 3 ADR and its causality during use of anti-fungal agents by WHO-UMC criteria *p-value= 0.96

ADR	Mucormycosis without orbital extension (n=59)		Mucormycosis with orbital extension patients (n=144)	
	Possible*	Certain	Possible*	Certain
Hypokalemia	11	0	31	0
Raised urea	1	0	3	0
Raised creatinine	11	0	21	0
Fever	12	0	25	0
Chills	11	0	27	0
Nausea	1	0	5	2
Vomiting	3	0	8	1
Thrombophlebitis	9	0	21	0

DISCUSSION

COVID-19 infection is limited to the acute phase but has consequences in patients who are immuno-compromised with a history of diabetes mellitus and use of glucocorticoids for long periods. Opportunistic infection with fungus-like mucor is very rare but due to above-mentioned reasons a large number of cases were reported during this pandemic [8].

In this study, we have observed that more than 50% of patients had a history of hospitalisation, oxygen therapy, diabetes mellitus, treatment with glucocorticoids and steam inhalation during their COVID-19 illness. All the patients received antibiotics and supplements like vitamins and zinc.

Pharmacotherapy was evaluated according to WHO core prescribing indicators. In both, the groups' mucormycosis with and without orbital extension, medicines prescribed per encounter exceed the optimal value 1.6-1.8. A large number of medicines were prescribed by generic name. The percentage of encounters with antibiotics and injectable were 100% which should be 20%-26.8%. All the medicines should be from the essential drug list which was around 90% [9].

Globally, the prevalence of mucormycosis varied from 0.005 to 1.7/million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India. India is already having the second largest population with Diabetes Mellitus (DM) [10]. On the other hand corticosteroids cause impairment in the migration, ingestion, and phagolysosomal fusion of bronchoalveolar macrophages. Diabetic patient and supplementation with steroid therapy make the patient vulnerable to mucormycosis. There are few case reports of mucormycosis resulting from short courses (5-14 days) of steroids [11].

In a systemic review conducted in 2021 of 101 patients with post-covid mucormycosis history of diabetes mellitus was present in 83.3%. History of corticosteroid intake for the treatment of COVID-19 was present in 76.3% of cases, followed by remdesivir (20.6%) and tocilizumab (4.1%). In this study, 61.1% of patients had a history of diabetes mellitus type-2, 66.7% and 33.3% patients received treatment with glucocorticoids and remdesivir respectively in patients of mucormycosis with orbital extension [8].

In a systematic review conducted during April 2021 by John et al. in 41 confirmed mucormycosis cases in patients with COVID-19, DM was present in 93% of cases, while 88% were receiving corticosteroids [12].

In a 2019 nationwide multi-centre study of 388 confirmed or suspected cases of mucormycosis in India before COVID-19, Prakash, et al. found that 18% had diabetic ketoacidosis and 57% of patients had uncontrolled DM [13]. History of diabetes mellitus and treatment with corticosteroids was present in more than half (50%) of the patients of mucormycosis in the present study which shows a reasonable relationship among them.

In a multi-centre observational study done by Patel, et al, out of 465 patients, amphotericin B was a primary stay of treatment in 81.9% and Posaconazole was prescribed in combination with it in 11.4% of patients [14]. In the present

study, 85.24% (52/61) patients received amphotericin B and 11.5% (7/61) patients received posaconazole which is quite similar to the above study.

In a study conducted by Kavita Sachdeva, et al. out of 110 patients with mucormycosis in 2021, the adverse drug reactions reported were shivering (42), fever (33), nausea and vomiting (6). In the present study, the most common adverse drug reaction reported was hypokalemia followed by chills [15,16].

Limitations of Study

1. Due to delay in approval from Institutional Ethics Committee initially when there was a peak in cases of mucormycosis, we were not able to enrol the patients during that time being
2. Due to the pandemic of COVID-19, only those patients who developed mucormycosis after recovering from COVID-19 infection were enrolled. Patients having co-infection were not included in the study

CONCLUSION

It was observed in the present study that patients who had a history of hospitalization, oxygen therapy, diabetes mellitus type-2 and steam inhalation had a high risk of post-COVID rhino-cerebral mucormycosis. In patients of mucormycosis, medicines prescribed per encounter exceed the optimal value given by WHO core prescribing indicators. Also, all the prescriptions contained antibiotics and injectable. Polypharmacy was observed. 85% of patients received conventional amphotericin B. Highest incidence of ADR observed during the use of anti-fungal agents was hypokalemia with causality possible according to WHO-UMC criteria.

DECLARATIONS

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of BJ Medical College and Civil hospital, Ahmedabad (EC/Approval/62/2021/01/06/2021).

Author Contributions

Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing-original draft preparation was done by Jagrit Shachi; writing-review and editing, visualization, supervision, project administration were done by Dumatar Chandresh B. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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