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Drug utilization study in covid associated mucormycosis patients in a tertiary care hospital

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Abstract

Background: Drug utilization research is essential for supporting rational, cost-effective use of drugs. In its wake, COVID-19 pandemic caused a surge in mucormycosis cases. Globally prevalence of mucormycosis was 0.005-1.7per million population, while it is nearly 80 times higher (0.14 per1000) in India compared to developed countries. Thus, present study was undertaken to assess prescription-patterns and drug-utilization by measuring WHO drug use indicators in Covid associated Mucormycosis patients.
Objectives: To study the prescribing patterns of drugs used in COVID associated mucormycosis, to evaluate prescriptions according to WHO Drug Use Indicators and to assess Adverse Drug Reactions if any.
Methods: Cross sectional, observational study. Data collected from files of patients admitted in the Mucormycosis ward of tertiary care hospital. Various parameters of utilization pattern were evaluated.
Results: Total numbers of files analyzed were 70 in which 947 drugs were prescribed. 74.76% drugs prescribed from NLEM. All drugs prescribed from the hospital pharmacy. Average number of drugs per prescription is 13.5. Most common drug prescribed-Amphotericin B (7.6%). Most common class was supplements (22.28%) followed by antibacterial (17.85%). The proportion of use of generic name was seen in 86.38%, branded-13.62%. Predisposing risk factors for covid associated mucormycosis like steroid use was found in 27.14% and 62.85% were diabetic. ADR with Amphotericin B was seen in 8.6% patients.
Conclusion: Mucormycosis spreads rapidly, prompt and appropriate treatments are necessary. Judicious use of drugs is warranted to prevent Covid Associated Mucormycosis. Increased vigilance in COVID-19 patients, even in those who have recovered is necessary.
Keywords: Drug utilization research, COVID-19, Liposomal Amphotericin B.

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1. Introduction

The World Health Organization (WHO) has defined drug utilization research as the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences. [1-2] It may be drug oriented, emphasizing the safety and effectiveness of drugs as well as utilization-oriented aiming to improve the quality of drug therapy through educational interventions. Drug utilization pattern needs to be evaluated from time to time so as to increase therapeutic efficacy, decrease adverse effects and promote rational and cost-effective drug use [3].

It is important to understand that inappropriate use of drugs pose risk of perils to the patients and an unnecessary expense [4]. Irrational and inappropriate use of drugs in

health care framework observed globally is a significant concern. [5,6]

Secondary infections are a well-described phenomenon in influenza, Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome, and other respiratory viral illnesses. However super-infections and co-infections in COVID-19 pneumonia are still under exploration [7]. Secondary infections are reportedly common in hospitalized, severely ill Covid-19 patients, encompassing between 10 and 30% of cases, fungal being 10 times more common [7]. As the nature of the disease is still not completely unveiled, it can't be confirmed if it's a complication of the disease or its management. Drugs like Corticosteroids i.e., Methylprednisolone and Dexamethasone are believed to modulate inflammation mediated lung injury and thereby reduce progression of respiratory failure [8] in Covid-19. Their side effects include increased secondary infections, immune modulation, and manifestation of latent diabetes mellitus, dizziness, weight gain, mood changes, and insomnia and muscle weakness [9]. Mucormycosis is amongst the most fulminant form of Zygormycosis caused by Mucorales species of the phylum Zygomycota[10] described as a potentially lethal infection occurring mostly in immunocompromised hosts, particularly in those with diabetes mellitus, leukemia and lymphoma[11].

The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment. [11] Given the rapid pace of scientific discovery and clinical data generated by the large number of people rapidly infected by SARS-CoV-2, clinicians need accurate evidence regarding effective medical treatments for this infection.

The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million populations [12]. Whereas, in Indian population its prevalence is 0.14 per 1000, which is about 80 times higher than developed countries [13]. The fatality rate of mucormycosis is 46% globally 13. However, factors like intracranial or orbital involvement, irreversible immune suppression increases fatality to as high as 50% to 80% [14]. A high suspicion for this disease must be considered in patients who are immune compromised. Tissue necrosis, a hallmark of mucormycosis is often a late sign [14]. Mucormycosis is a life-threatening invasive fungal infection most commonly observed in immunocompromised patients. Throughout the COVID-19 pandemic, a growing number of Mucorales associated infections, now termed COVID-19 associated mucormycosis (CAM), have been reported. [15]

Early diagnosis, prompt institution of appropriate antifungal therapy, surgical debridement whenever necessary, knowledge of risk factors and their timely reversal is the key for management. Thus, a study was undertaken to study prescribing patterns in Covid associated mucormycosis, and to find out adverse drug reactions if any.

1.2 Objectives of the study:

1) To study the prescribing patterns of drugs used in COVID associated mucormycosis.
2) To evaluate prescriptions according to WHO Drug Use Indicators.
3) To assess Adverse Drug Reaction if any.

2. Materials and methods

2.1 Study Design: Cross-sectional observationalstudy.

2.2 Study Area: Mucormycosis ward of Tertiary Care Institute.

2.3 Study population: Patients admitted in the Mucormycosis wardof Tertiary Care Institute.

2.4 Sample size: No. of cases admitted in mucormycosis ward from May 2021 to June 2021. Their prescriptions with established diagnosis of COVID associated mucormycosis will be assessed.

2.5 Selection Criteria:

a) Inclusion criteria: Patients with COVID associated Mucormycosis admitted in Ward.

b) Exclusion Criteria: Patients with Mucormycosis not associated with COVID.

Patients not willing to consent

2.6 Study Duration: Two months (May 2021 to June 2021)

2.7 Methodology: Institutional ethics committee approval taken. Confirmed mucormycosis patients will be considered. Patient satisfying inclusion criteria will be included. Informed consent will be taken. Demographic profile, prescription pattern and Adverse Drug Reaction if any will be recorded.

The prescriptions will be analyzed for following parameters:

- **Demographic Details**: - The variables that were assessed from the prescriptions included the demographic profile-Gender, Age
- **WHO Drug Use Indicators**:

1) Prescribing Indicators:

a) Total number of prescriptions
b) Average number of drugs per prescription
c) Percentage of encounters with an injection prescribed
d) Percentage of drugs prescribed from the National List of Essential Medicines (NLEM)
e) Percentage of drugs prescribed by generic name and branded name
f) Percentage of drugs dispensed from hospital pharmacy

g) Percentage of fixed dose combination (FDC)

h) Percentage of polypharmacy

2) Patient Indicators:

a) Total number of female & male patients.

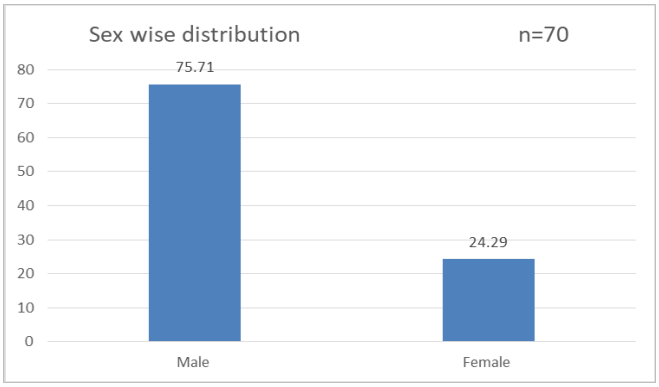
b) Average age of male & female patients

2.8 Statistical analysis:

The data will be analyzed using descriptive statistics (MS Excel software).

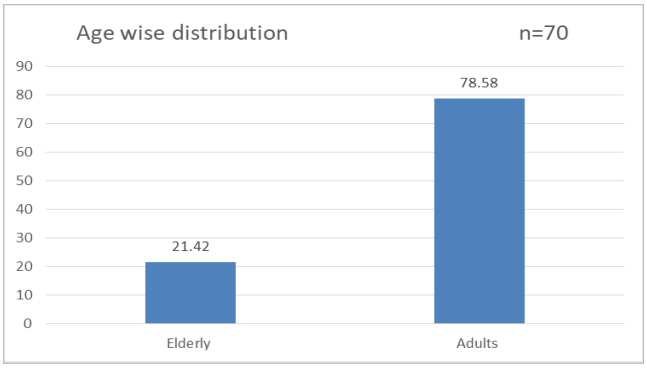
3. Results

Figure 1: Sex wise distribution



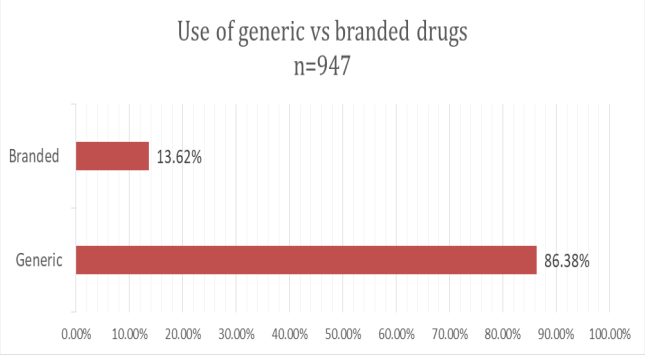
Males constituted majority (75.71%) and females (24.29%)

Figure 2: Age wise distribution



Age wise distribution of patients shows majority of the patients were adults aged between 21-65 years of age (78.58%) followed by elderly (21.42 %)

Figure 3: Use of generic vs branded drugs



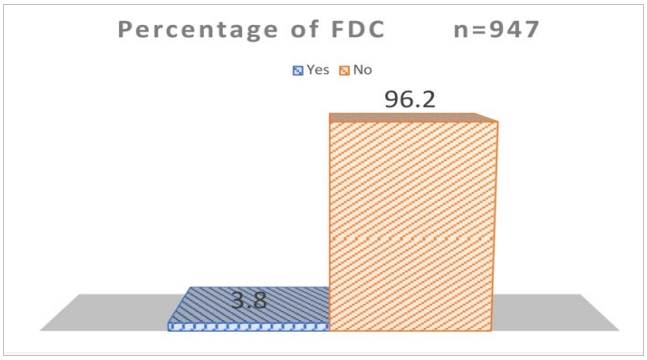
The proportion of use of generic name was seen in majority (86.38%) as compared to branded (13.62%).

Table 1: Number of drugs prescribed per prescription

No. of drugs/ prescription	Total No
One	0
Two	0
Three	0
Four	0
Five	0
Six	1
Seven	2
Eight	2
Nine	1
Ten	6
Eleven	3
Twelve	12
Thirteen	7
Fourteen	10
Fifteen	6
Sixteen	15
Seventeen	2
Eighteen	0
Nineteen	0
Twenty	0
Twenty-one	1
Twenty-two	0
Twenty-three	0
Twenty-four	2
Total	70

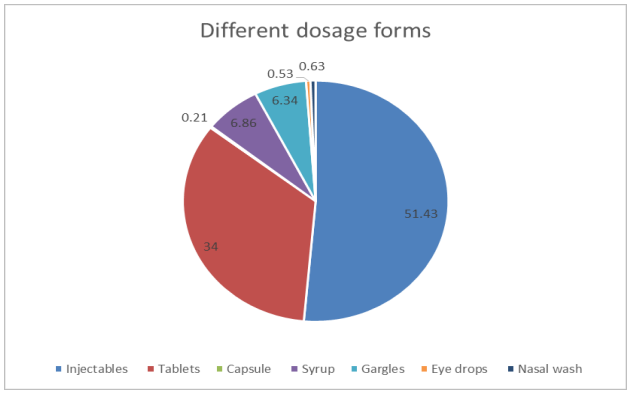
Average number of drugs per prescription was 13.5. Maximum number of prescriptions 15 had 16 drugs prescribed.

Figure 4: Percentage of FDC



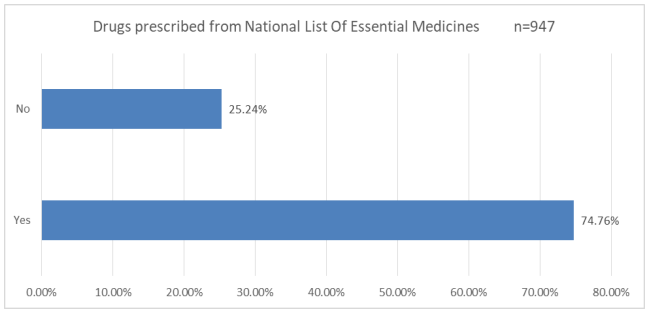
3.8% of the drugs were fixed dose combinations.

Figure 5: Different dosage forms



It was seen that injectables (51.43%) were used in majority followed by tablets (34%). Eye drops were used least (0.53%). Among the injectables, most commonly prescribed was liposomal amphotericin B (14.78%)

Figure 6: Drugs prescribed from National List Of Essential Medicines



74.76 % of the drugs were prescribed from National List of Essential Medicines. All the drugs were prescribed from the hospital pharmacy.

Table 2: WHO Drug Use Indicators

Type of prescribed doses	Total
Total number of prescriptions	70
Total number of drugs	947
Average no of drugs/ prescription	13.5
% of drugs dispensed from hospital pharmacy	100%
% of frequency of therapy	100%
% of poly pharmacy≥5 drugs	100%
% of drug from NLEM	74.76%
% of prescribed by brand name	13.62%
% of prescribed by generic name	86.38%

Table 3: Drug utilization pattern

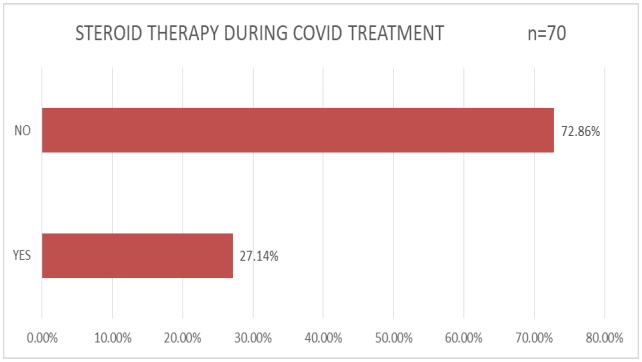
Dosage forms	Drugs	Total (n=947)	%
Injectables	Amoxicillin + clavulinic acid	17	1.80
	Cefexime	1	0.11
	Ceftazidime	50	5.28
	Cefotaxime	31	3.27
	Frusemide	2	0.21
	Insulin	56	5.91
	Potassium chloride	68	7.18
	Amphotericin B	72	7.60
	Low mol weight heparin	4	0.42
	Ceftriaxone	14	1.48
	Metronidazole	34	3.59
	Pantoprazole	67	7.07
	Ondansetron	66	6.97
	Piperacillin + tazobactam	5	0.53
Tablet	Atorvastatin	8	0.84
	Amoxicillin + clavulinic acid	13	1.37
	Aceclofenac + paracetamol	32	3.38
	Aspirin	17	1.80
	Amlodipine	18	1.90
	Cetrizine	65	6.86
	Clopidogrel	3	0.32
	Diclofenac	2	0.21
	Enalapril	1	0.11
	Fluconazole	1	0.11
	Ferrous sulphate + Folic Acid	2	0.21
	Glimiperide	4	0.42
	Losartan	3	0.32
	Metformin	20	2.11
	Metronidazole	2	0.21
	Multi Vitamin B Complex	70	7.39
	Paracetamol	56	5.91
	Posaconazole	2	0.21
	Ramipril	2	0.21
	Rivoroxaban	1	0.11
Capsule	Doxycycline	2	0.21
Syrup	Posaconazole	65	6.86
Gargles	betadine	60	6.34
Eye drops	Hydroxypropyl methyl cellulose	5	0.53
Nasal wash	Sodium bicarbonate + Sodium chloride	6	0.63

Table 4: Class wise distribution of the drugs:

Drug Class	Total	Percentage
Antibacterial	169	17.85
Antifungal	140	14.78
Antiemetic	66	6.97
Antidiuretics	2	0.21
Antihistaminic	65	6.86
Anticoagulant	8	0.84
Antidiabetic	80	8.45
Hypolipidemic agent	8	0.84
Antihypertensive agent	24	2.53
Proton pump inhibitors	67	7.07
NSAIDs	107	11.30
Supplements	211	22.28

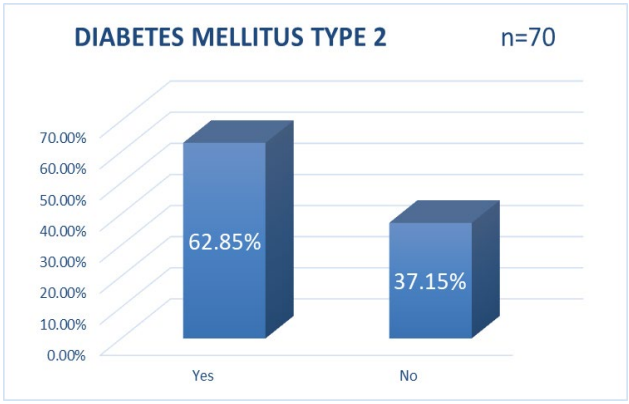
Class wise distribution of the drugs show that supplements (22.28%) were most commonly prescribed followed by anti-bacterial (17.85 %) and anti-fungal (14.78 %).

Figure 7: Steroid therapy received during covid treatment



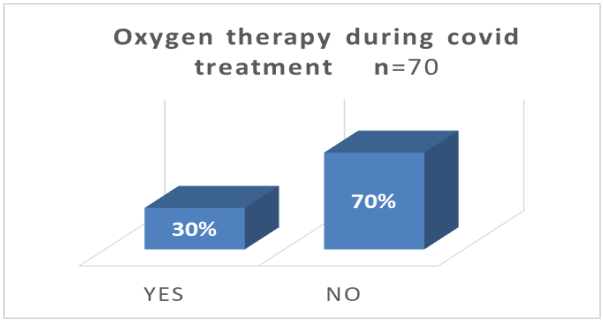
27.14% patients had received steroid therapy during covid treatment.

Figure 8: Known cases of Diabetes Mellitus Type 2



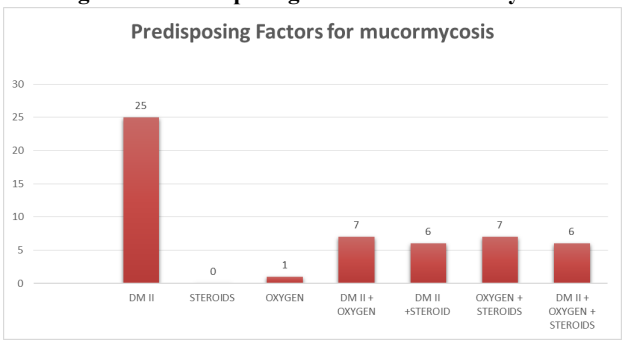
62.85% were known cases of Diabetes Mellitus Type 2

Figure 9: Patients that received oxygen therapy during covid treatment



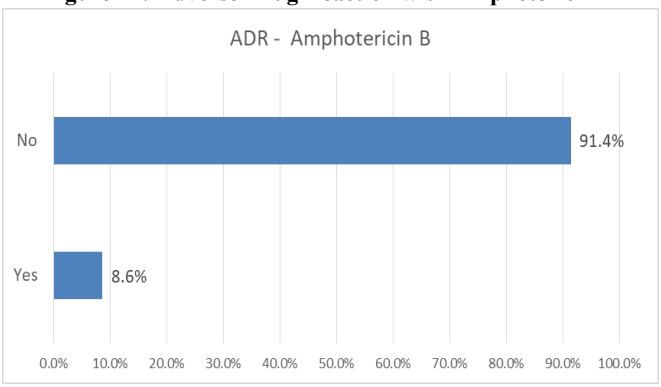
30% patients had received oxygen therapy during covid treatment

Figure 10: Predisposing factors for Mucormycosis



Diabetes Mellitus was the most common predisposing factor.

Figure 11: Adverse Drug Reaction with Amphotericin B



6 patients out of 70 had ADR to Amphotericin B (8.6% of patients)

4. Discussion

The second wave of COVID -19 led to panic in many countries, including India and some parts of the world suffering from the third wave. As this infection had high mortality, supportive care equipments such as oxygen cylinders, ventilators and heavy use of steroids play a vital role in the management of COVID-19. The consequential immunosuppression, former co-morbidities and its medications have made the patients susceptible to secondary fungal infections such as Mucormycosis. The COVID-19 affected patients who are more susceptible to these infections are immunocompromised, have diabetes, and are prescribed heavy steroids.

In a study by Prakash and Chakrabarti, the main risk factor was noted as diabetes mellitus 73.5% which was similar to our study where 62.85% patients were diabetic. [15]

In a study by A. Dilek *et al* 76% were male which is similar to our study where 75.71% were males. The most commonly seen risk factors were corticosteroid use (90.5%) and diabetes (79%) in their study but in our study patients with diabetes 62.85% and steroid use was 27.14%.[16]

In current practice, amphotericin B and isavuconazole are the 2 antifungal agents licensed by the US Food and Drug Administration (FDA) for the primary therapy of mucormycosis. First-line treatment is with an amphotericin derivative, preferably the liposomal form of amphotericin B to minimize nephrotoxicity. Other options include amphotericin B deoxycholate, isavuconazole, and posaconazole. In patients with extensive disease or rapid progression, the addition of posaconazole or isavuconazole to amphotericin B may be considered [17] Liposomal amphotericin B is the first choice of treatment[18] in patients with intracranial extension as it crosses the blood–brain barrier more effectively. Posaconazole can be used for salvage treatment of mucormycosis in patients intolerant to amphotericin B. It has also been used as step-down therapy after initial control of the disease with amphotericin.

Surgery and Injectable Amphotericin B can significantly improve prognosis. Control of underlying disease, systemic antifungal medication and surgical debridement proved to be the mainstay of mucormycosis treatment. [19-20]

Adverse Drug Reaction

Intravenous amphotericin B is the most important drug for salvage therapy. In a study done by Kavita *et al*, out of the 110 patients who received liposomal Amphotericin B injection, 2 patients developed adverse drug reaction and 110 patients received Amphotericin B Lipid complex in which 7 patients developed adverse drug reaction, which was similar to our study, where out of 70 pts 2 patients developed adverse drug reaction to liposomal Amphotericin B and 6 to Amphotericin B Lipid complex. All of them developed chills, and rigor within minutes of drug administration and got subsided with the administration of avil and hydrocortisone. In our study the drug was then discontinued and patient was started on Posaconazole. [21]

Preventive measures

Aiming for better glycemic control in those with diabetes, appropriate use of systemic corticosteroids and prevention of unnecessary use of antibiotic, antifungal and other immunomodulators. Sterilization and disinfection of the equipment used by multiple patients (tracheal tubes, ventilators), ventilation systems (if there is poor ventilation in the hospital that can contribute to dampness and dust); Proper wound management (bandage, tape, adhesives, including tapes to secure medical devices such as endotracheal tubes, ostomy devices must be sterilized and changed regularly); Proper management in health facilities. [22]

DUS gives an insight into patterns and determinants of drug use. The WHO core drug use indicators were used to primarily describe the drug use, particularly the prescribing indicators. [23]

Limitations

Small sample size. Studies with greater sample size need to be undertaken.

5. Conclusion

Drug utilization studies on mucormycosis are few with none particularly on Covid Associated Mucormycosis. Our study was an attempt to describe the drug prescribing pattern of covid associated mucormycosis in a tertiary care teaching hospital.

DUS is vital part of pharmacoepidemiology. Therefore, periodical auditing of drug utilization pattern is crucial for promotion of rational use of drugs, for increasing the therapeutic efficacy and the cost effectiveness, for decreasing the adverse effects and to provide feedback to the prescribers. Judicious use of drugs is warranted to prevent CAM. Increased vigilance in COVID-19 patients, even those who have recovered is necessary.

Conflict of Interest: Nil

Source of funding: Nil

Institutional Ethics Committee approval no: ND Dept 0521164-164

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