

Drug Utilization Study in Patients with COVID-19 Associated Mucormycosis in a Tertiary Care Hospital, South India

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Abstract

COVID-19 associated Mucormycosis (CAM) is a serious condition in India considering its unprecedented surge due to COVID-19 and associated high morbidity and mortality. Diabetes and widespread usage of steroids in a background of COVID-19 appear to increase the risk of CAM exponentially. Management includes control of the underlying disease or risk factor, strict glycemic control, surgical debridement of necrotic infected tissue, and specific antifungal therapy. First-line antifungal treatment consists of intravenous liposomal Amphotericin-B (LAB) or deoxycholate Amphotericin-B (AMB) and second-line antifungals are intravenous (IV) or oral Posaconazole (POS) which can also be used as salvage therapy. This study is conducted to observe the drug utilization pattern in CAM patients in tertiary care hospital in South India.

A prospective, observational study of 55 patients admitted with CAM are studied in terms of drug usage. POS (98.2%) is the most used drug followed by intravenous AMB (49.1%). POS-Oral are used in 83.6 %, POS-IV in 49.1% and AMB-retrobulbar is used in 12.7% of the patents and average doses are within recommended limits. Anti-bacterial and other antifungal are used in 12.7% and 1.8% of the patients respectively, and 34.5% underwent debridement surgery. Though LAB is the recommended 1st line treatment, AMB and POS are used as a reasonably accepted alternative. Guidelines and recommendations should consider cost, compliance (availability of oral formulations), safety profile, and accessibility aspects which suit the needs of Low- and middle-income countries (LMIC) especially during an unprecedented event like COVID-19 and CAM.

Keywords: Drug utilization study, COVID-19 associated Mucormycosis, Amphotericin-B, Posaconazole

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Introduction

India reported the highest number of CAM cases in the world, and the prevalence is estimated to be 80 times higher compared to that of the developed countries [1]. Earlier reports of isolated cases started coming in since September 2020 and by May 28, 2021, at least 14,872 cases have been found in India [2,3]. Prevalence of CAM is reported to be 0.27% among hospitalized COVID-19 patients and the rates are higher in patients managed in intensive care unit (ICU) than in general ward [4].

The usual risk factors for Mucormycosis are diabetes (DM), neutropenia, hematological malignancies, organ transplantation, trauma and burns, and use of immunosuppressant drugs. Uncontrolled diabetes, particularly in patients having ketoacidosis, is a strong and independent predisposing factor for Mucormycosis [5] and Rhino-orbital-cerebral Mucormycosis (ROCM), occurs almost exclusively in people with diabetes [6]. Similarly, corticosteroids induce immune suppression and predisposes to opportunistic infections including Mucormycosis. Diabetes and widespread usage of steroids in a background of COVID-19 appear to increase the risk of CAM exponentially [1]. Figure.1 shows the mechanisms by which “The Demonic “Trident” of Diabetes, steroids and COVID-19 predispose to CAM [7].

Patients with CAM most commonly present with ROCM, followed by pulmonary disease and less commonly as gastrointestinal disease, with or without CNS involvement [8]. The treatment of CAM is similar as treatment of patients with invasive Mucormycosis in other risk groups. Important aspects of management are control of the underlying disease or risk factors, strict glycemic control, surgical debridement of necrotic infected tissue, and

specific antifungal therapy [8,9]. First-line antifungal treatment consists of intravenous liposomal Amphotericin-B (LAB) or deoxycholate Amphotericin-B (AMB); second-line agents are intravenous or oral Posaconazole (POS) and Isavuconazole (ISA), which can also be used as salvage therapy [9]. Mortality rates for ROCM range from 40 to 80% depending on underlying conditions⁹ and, early diagnosis and prompt treatment are crucial, as a delay of even 6 days is associated with a doubling of mortality [10]. Drug utilization studies evaluate the present state and anticipate future trends of drug usage, estimate drug expenditures, appropriateness of prescriptions and adherence to evidence-based recommendations [11].

Material and Methods

Prospective, observational study of patients admitted with CAM to observe the drug utilization pattern. Permission was taken from Institutional Ethics Committee, study was conducted in accordance with the principles of Good Clinical Practice (ICH-GCP), and a written informed consent was signed by all the study participants. Demographic details, medical history, COVID-19 treatment details, treatment for CAM, adverse effects were collected from the treating notes. Data entry and statistical analysis are performed with Microsoft excel 2010 and SPSS (Statistical package for the Social Sciences) version 19.

Results

A total of 55 patients of CAM are studied. The demographic details are presented in table 1. Most of the patients are males (78.2%) and most had DM (72.7%) as comorbidity followed by Hypertension (HTN) (20%). Most common presentation is

Mucormycosis with sinus involvement (RS) (45.5%) followed by Rhino-orbital Mucormycosis (ROM) (25%) and ROCM (25%).

The details of treatment are given in table 2. Posaconazole (POS) (98.2%) is the most used drug followed by AMB (49.1%). POS-Oral are used in 83.6 %, POS-IV in 49.1% and

retrobulbar Amphotericin-B (AMB-RB) is used in 12.7% of the patents. The pattern of drug combinations is given in table 3 and represented in a Venn diagram in figure.2. Antibacterial and other antifungal agents are used in 12.7% and 1.8% of the patients respectively, and 34.5% underwent debridement surgery.

Table 1: Demographic details of patients with COVID-19 associated Mucormycosis

N=55	Mean (SD, Min-Max) or n (%)
Age in years	51.8 (\pm 14.3, 24 - 80)
Gender	
Males	43 (78.2%)
Females	12 (21.8%)
Comorbidities	
DM	40 (72.7%)
HTN	11 (20%)
Both DM and HTN	7 (12.7%)
Epilepsy	2 (3.6%)
Mucormycosis	
RS	25 (45.5%)
ROM	14 (25.5%)
ROCM	14 (25.5%)
ROCMC	2 (3.6%)

DM: Diabetes mellitus, HTN: Hypertension, RS: Mucormycosis involving sinus, ROM: Rhino-orbital-Mucormycosis, ROCM: Rhino-orbital-cerebral Mucormycosis, ROCMC: Rhino-orbital-cerebral Mucormycosis with candidiasis

Table 2: Details of treatment of patients with COVID-19 associated Mucormycosis

N=55	n (%)
Pharmacological Treatment	
Posaconazole	54 (98.2%)
• Posaconazole-Oral	46 (83.6%)
• Posaconazole-IV	27 (49.1%)
Amphotericin-B-IV	27 (49.1%)
Amphotericin-B-retrobulbar	7 (12.7%)
Other anti-fungal	1 (1.8%)
Antibacterial	7 (12.7%)
Surgery	19 (34.5%)

IV: Intravenous

Table 3: Pattern of drug combinations in patients with COVID-19 associated Mucormycosis

Drug combination (N=55)	n (%)
AMB-IV+ POS-Oral	21 (38.2%)

AMB-IV+ POS-IV	14 (25.5%)
AMB-IV+ POS-IV+ POS-Oral	8 (14.5%)
POS-IV+ POS-Oral	19 (34.5%)
AMB-RB+AMB-IV	7 (12.7%)
AMB-RB+POS-IV	4 (7.3%)
AMB-RB+POS-Oral	4 (7.3%)
AMB-RB+AMB-IV+POS-Oral	4 (7.3%)
AMB-RB+AMB-IV+POS-IV	4 (7.3%)
AMB-RB+ POS-IV+ POS-Oral	1 (1.8%)
AMB-RB+AMB-IV+ POS-IV+ POS-Oral	1(1.8%)

AMB-IV: Amphotericin-B intravenous, AMB-RB: Amphotericin-B retrobulbar, POS-Oral: Posaconazole Oral, POS-IV: Posaconazole intravenous

Table 4: Details of drug dosage and duration in patients with COVID-19 associated Mucormycosis

Drug, dosage, and duration	Mean (SD, min-max)
Posaconazole-Tablet Dosage (mg/day)	391.3 (\pm 139.5, 300-600)
Posaconazole-Tablet Duration (days)	7.5 (\pm 6.1, 1-28)
Posaconazole-IV Dosage (mg/day)	300.0 (\pm 0.0, 300-300)
Posaconazole-IV Duration (days)	6.5 (\pm 3.4, 1-14)
Amphotericin-B-IV Dosage (mg/day)	300.0 (\pm 0.0, 1-14)
Amphotericin-B-IV Duration (days)	6.3 (\pm 5.0, 2-20)
Amphotericin-B-Retrobulbar Dosage (mg/day)	2000.0 (\pm 0.0, 2000-2000)
Amphotericin-B-Retrobulbar Duration (days)	1.0 (0.0, 1-1)
Anti-Bacterial Duration (days)	6.1 (\pm 2.6, 2-10)

IV: Intravenous

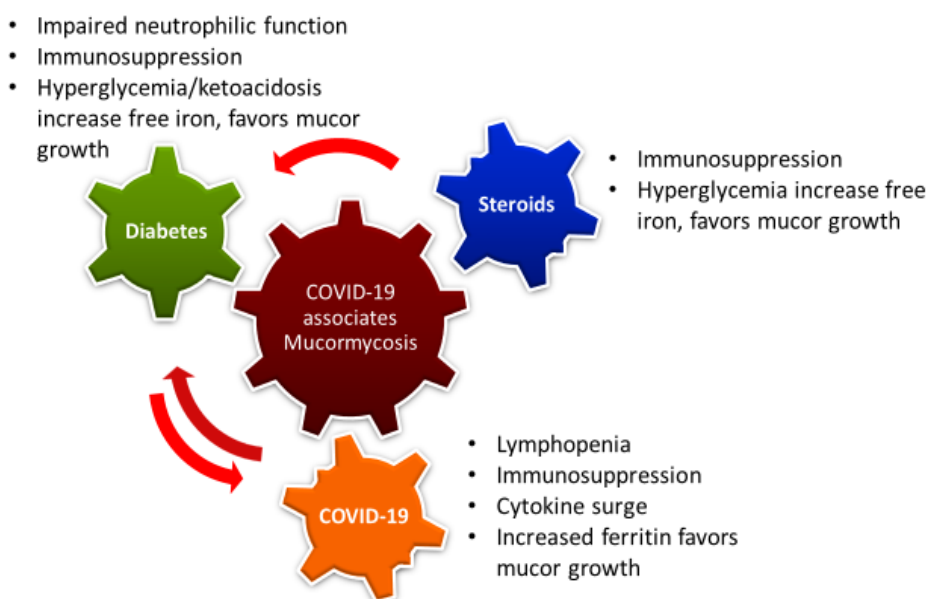


Figure 1: Mechanisms of “The Demonic Trident” of Diabetes, steroids and COVID-19 predisposing to COVID-19 associated Mucormycosis”

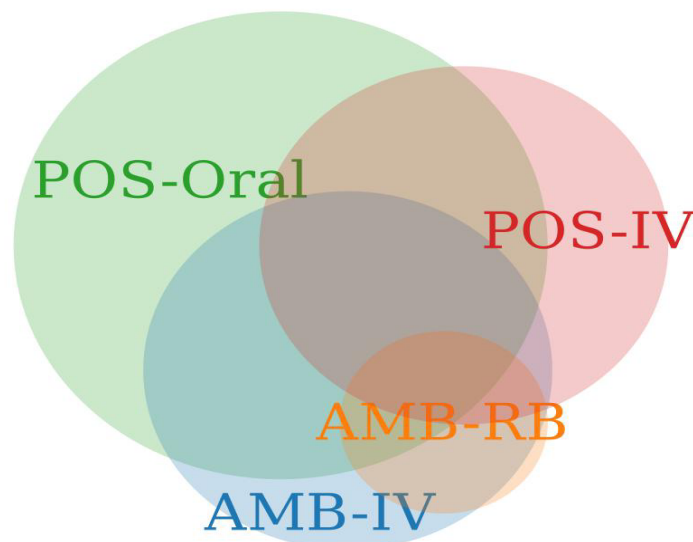


Figure 2: Pattern of drug combinations used

NB: Size of the circle is proportional to number of patients.

POS-Oral: Posaconazole Tablet, POS-IV: Posaconazole intravenous, AMB-IV: Amphotericin-B intravenous, AMB-RB: Amphotericin-B retrobulbar.

Details of dosage and duration are given in table 4. Average dose of POS-Oral, POS-IV, AMB-IV and AMB-RB are 391.3 mg (± 139.5), 300 mg, 300 mg and 2000 mg respectively, whereas the average duration of treatment are 7.5 days (± 6.1), 6.5 days (± 3.4), 6.3 days (± 5.0) and 1 day respectively.

Common Antibacterials used are Ceftriaxone (5 patients), Piperacillin-Tazobactam (1 patient) and Meropenem (1 patient). Mean duration of Antibacterial is 6.1 days (± 2.6). Other antifungal agents used are Fluconazole (1 patient). Surgery performed is Endoscopic debridement with either sinus antral wash or abscess drainage or exenteration/decompression (if orbital).

Discussion

The three important aspects of treatment of CAM are control of the underlying disease or risk factor, surgical debridement of necrotic infected tissue, and specific antifungal therapy [9].

The recommended first-line treatment of CAM is high-dose LAB. Due to the potential for toxicity especially on kidney and infusion

reactions, AMP is used only if cost and availability of LAB is an issue [12,13]. In patients who are intolerant to AMB, alternative agents are POS or Isavuconazole (ISA), which can be used as salvage therapy also. These are also used in refractory mycosis often combined with LAB. Antifungal therapy may be initiated with LAB and POS, followed by ISA as salvage therapy [14,15]. A recent review of 80 cases from 18 countries found that systemic antifungals were given in more than 95% of them in which AMB was most used (89%). POS was used along with AMB in patients with ROCM. Isavuconazole was used in five patients, either in combination with AMB (two patients), as salvage therapy (two patients), or as monotherapy (one patient) [8]. Present study reflects similar usage pattern, but LAB and ISA are not used considering cost and availability issues.

The preferred regimen of LAB is 5 mg/kg/day, dilute in 200 ml 5% dextrose over 2-3 hrs infusion and a higher dose of 10 mg/kg/day may be given if orbito-cerebral involvement (ROM, ROCM). AMB is an

equivalent alternative to LAB in terms of the efficacy profile but has limitations in terms of safety. The recommended dose of AMB is 0.7 mg/kg/day [16]. The doses given in present study for AMB, POS-IV, POS-Oral are in line as that of earlier studies and guideline recommendations [17]. The recommended duration depends on the seriousness of the disease. For more severe forms like ROCM, 4 weeks of induction with LAB followed by oral drugs for a minimum of 6 weeks till 3-6 months depending on the regression.

The duration in the present study roughly can be estimate as 2-3 weeks considering the given drug regimen as per figure. 2. The average duration for AMB, POS-IV, POS-Oral is 6-7 days, and cannot be compared, as follow up data is not collected from these patients. A shorter duration of antifungal therapy (versus a longer duration), and treatment with AMB deoxycholate (versus LAB) were independent risk factors of mortality. Factors like treatment modality, drug choice, dosage and duration must be taken into consideration for better prognosis. A combined medical and surgical management was associated with a better survival [18].

In low- and middle-income countries including India, Mucormycosis is associated with high mortality (45%–90%) [19,20]. The probable reasons include a delay in diagnosis, accessibility of drugs, and the high cost of managing Mucormycosis.

Gathering knowledge of practical management of tailoring to local needs is a short notice was a challenge among clinicians in low-income and middle-income countries [18].

Guidelines and recommendations should consider cost, compliance and accessibility aspects which suit the needs of Low- and middle-income countries (LMIC) especially during an unprecedented event like COVID-19 and CAM.

Conclusion

Though the recommended 1st line treatment for CAM is LAB/AMB, POS is accepted as a reasonable alternative considering cost and availability of oral preparation. Drug choice, dosage and duration are important for better prognosis. Guidelines and recommendations should consider cost effectiveness, compliance and accessibility aspects matching the needs LMIC countries especially during an unprecedented event like COVID-19 and CAM.

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