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LIPOSOMAL AMPHOTERICIN B INDUCED HYPOKALEMIA ANDRENAL TOXICITY IN MUCORMYCOSIS PATIENTS- A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Introduction: Rhinocerebral mucormycosis, an aggressive and often fatal fungal infection, predominantly affects immunocompromised individuals. Liposomal Amphotericin B (L- AMB) is a preferred treatment due to its reduced nephrotoxicity compared to conventional Amphotericin B. Despite its benefits, L-AMB is associated with potential hypokalemia and renal toxicity, which necessitates careful monitoring. **Methods:** This retrospective observational study examined 40 patients diagnosed with mucormycosis and treated with L-AMB from May 2021 to August 2021 at Continental Hospitals, Hyderabad. The objectives were to evaluate the prevalence of hypokalemia, monitor creatinine levels for nephrotoxicity, assess survival rates, and evaluate the risk associated with diabetes. **Results:** Of the 40 patients, 38 tested positive for mucormycosis and were treated with L-AMB and potassium supplements. The cohort had a median age of 47.5 years, with a male-to-female ratio of 8.5:1. Hypokalemia was prevalent, with serum potassium levels significantly dropping after 3 days of treatment (average initial: 4.1 mmol/L; after 3 days: 3.3 mmol/L; final: 3.6 mmol/L). Creatinine levels exhibited minor fluctuations with no significant long-term increases (average initial: 0.9 mg/dL; after 3 days: 1.0 mg/dL; final: 0.9 mg/dL). Diabetes was a major predisposing factor, with a higher survival rate observed in patients treated with L- AMB (84% survived). **Discussion:** The study highlights that while L-AMB effectively treats mucormycosis, it frequently induces hypokalemia. Renal function, however, remained relatively stable, demonstrating the relative safety of L-AMB regarding nephrotoxicity. Careful monitoring and timely potassium supplementation are essential in managing these adverse effects. **Conclusion:** L-AMB treatment for mucormycosis is associated with significant hypokalemia but minimal renal toxicity. Regular monitoring of electrolyte levels and renal function is crucial for optimizing patient outcomes and managing potential side effects.

KEYWORDS: Mucormycosis, Invasive fungal infection, Liposomal Amphotericin B, Hypokalemia, Renal Toxicity, Immuno-compromised.

INTRODUCTION

Mucormycosis

Rhinocerebral mucormycosis is a rare but often fatal condition characterized by an aggressive necrotizing infection due to fungi of the Mucoraceae family, spreading from the nose to the paranasal sinuses, orbit and hence to the central nervous system. The organisms are ubiquitous hence spores are easily inhaled and reach the nasal mucosa. The organisms are found in bread and fruit moulds and can be seen in nasal, throat and stool cultures of healthy subjects. Invasion requires the host defences to be compromised, and some debilitating illness is identified in over 95 per cent of cases. The commonest predisposing factor is diabetes mellitus, usually ketoacidosis, since glucose, ketones and low pH enhance fungal invasion and growth.[1]

Clinically, it can involve different regions which include rhino-orbito-cerebral, cutaneous, pulmonary, gastrointestinal, and disseminated (involving 2 or more regions). Rarely, it may be isolated from a single organ as well (renal/lymph node/parotid/ear/heart). Early diagnosis is the key to treatment and management approaches including prompt antifungal therapy, surgical debridement, and addressing the underlying predisposing condition.[2]

Mucormycosis typically occurs in patients with leukemia, with solid-organ transplants or bone marrow transplants, with diabetic ketoacidosis, in those who have received steroids or are neutropenic, and after desferioxamine therapy.[3]

The cumulative burden ranged between 137,807 and 208,177 cases, with a mean of 171,504 (SD: 12,365.6; 95% CI: 195,777–147,688) and mean attributable mortality at 65,500 (38.2%) deaths per year. The data indicates that the estimated prevalence of mucormycosis in India is nearly 70 times higher than the global data, which were estimated to be at 0.02 to 9.5 cases (with a median of 0.2 cases) per 100,000 persons.[4]

Only 6 to 10% of cases occur in subjects with no underlying disease. In contrast, in developing countries, most cases of mucormycosis occur in persons with poorly controlled diabetes mellitus or in immunocompetent subjects following trauma. Mucormycosis exhibits a marked propensity to invade blood vessels, leading to thrombosis, necrosis, and infarction of tissue. Mortality associated with invasive mucormycosis is high (> 30–50%), with 90% mortality associated with disseminated disease. Mortality rates are much lower, though still significant (10–30%), among patients with localized cutaneous disease.[5]

Liposomal amphotericin b

Invasive fungal infection is a major cause of morbidity and mortality in immune-compromised patients. Early diagnosis is the key to treatment and management approaches including prompt antifungal therapy, surgical debridement, and addressing the underlying predisposing condition. In most situations, intravenous amphotericin B is used as the first line of antifungal treatment, with the liposomal form being less nephrotoxic than the conventional form, and thus possible to be given for longer periods.[2] Amphotericin B (AMB) possesses broad-spectrum antifungal activity and well-documented efficacy against Candida, Aspergillus and Cryptococcus infections. Liposomal-AMB (L-AMB), which was developed as a drug delivery system for AMB to reduce its adverse events (e.g., nephrotoxicity), is prefered over AMB and is commonly used in clinical practice worldwide.[6]

Amphotericin B is a polyene antifungal agent with a broad range of activity against yeasts andmolds, as well as the protozoan parasite *Leishmania* spp. AmB binds to ergosterol in the fungal cell membrane leading to ion leakage and cell death. The initial formulation was amphotericin B deoxycholate (DAmB), which was developed in the 1950s. For many decades DAmB was the main antifungal agent available for the treatment of invasive fungal diseases. However, the significant dose-limiting toxicity of DAmB (most notably nephrotoxicity and infusion-related reactions) provided the impetus to develop new less toxic formulations. Liposomal amphotericin B (AmBisome®; LAmB) is a unique lipid formulation of amphotericin B that has been used for nearly 20 years to treat a broad range of fungal infections. While the antifungal activity of amphotericin B is retained following its incorporation into a liposome bilayer, its toxicity is significantly reduced.[7]

Liposomal Amphotericin B has improved therapeutic index, most likely due to its uptake by macrophages. These cells deliver the drug-lipid complex to the site of infection bypassing uninvolved tissues such as the kidneys. The drug containing spheres are subsequently disrupted mainly after attachment to the fungal cell wall, thereby releasing the drug into the fungal cells. Tissue concentration of liposomal Amphotericin B therefore varies significantly between different body organs, being lower in kidneys and higher in the macrophage rich reticular endothelial cells (Boswell et a`l., 1998).[8]

Amphotericin B in mucormycosis

Amphotericin B — Infusion-related reactions, particularly nausea, vomiting, chills, and rigors, are common with intravenous (IV) amphotericin B deoxycholate administration and usually occur either during infusion (within 15 minutes to 3 hours following initiation) or immediately following administration of the dose. Patients with infusion-related reactions may be pretreated with acetaminophen, or corticosteroids administered approximately 30 minutes before infusion.

Amphotericin B is associated with renal insufficiency, hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia. Thus, patients treated with amphotericin B should have daily monitoring of serum creatinine and electrolytes. Many patients require significant amounts of potassium and/or magnesium supplementation during therapy and hydration with normal saline during amphotericin B infusions. A more detailed discussion of the adverse effects of amphotericin is presented elsewhere.[5]

AMB may induce nephrotoxicity through tubular injury or renal vasoconstriction Tubular injury may be induced by intra membranous pore formation or vacuolation of the epithelial cells in the distal convoluted tubule, vasoconstriction may be induced by direct vasoconstrictor effects that might be initiated by the depolarization-induced opening of calcium channels. Tubular injury may, in part, be responsible for L-AMB-induced hypokalemia. Tubular injury may lead to increased permeability of the distal convoluted tubule and a subsequent increase in urinary potassium secretion through tubular Na+, K+-ATPase. In addition, tubular injury may result in a defective the distal tubule H+, K+-ATPase, or renal tubular acidosis, causing increased potassium elimination.[7]

The use of amphotericin B in this condition began in the early 1960s, but its toxicity is a majordrawback. The drug is fungistatic and needs to be given for at least two months, usually at doses of around 0.5-1 mg/kg on alternative days. Unfortunately renal impairment can occur at these doses, especially as most cases are debilitated from the outset.Other toxic effects include hypokalaemia, hepatic impairment, fever and chills.[2]

This study was conducted to address the gap in

understanding the impact of L-AMB on electrolyte imbalances and renal function, specifically focusing on hypokalemia and renaltoxicity.

The primary aim was to evaluate the prevalence of hypokalemia and its management in patients receiving L-AMB for mucormycosis. Objectives included assessing changes in serum potassium levels and renal function over the treatment course, analyzing survival rates, and understanding the implications for diabetic patients.

MATERIALS AND METHODS

This study is an observational retrospective study which was conducted on 40 patients who were diagnosed with mucormycosis and treated with Liposomal Amphotericin B with past history of COVID 19 infection. Study was conducted for a period of 4 months (May 2021 to August 2021) at Inpatient Department, Continental Hospitals Hyderabad.

The objectives of our study were as follows

1. To evaluate the prevalence of hypokalemia in patients with Mucormycosis receiving injection L-AMB
2. To evaluate the creatinine levels to monitor the nephrotoxicity associated with L-AMPB
3. To access the survival rates in patients treated with L-AMP
4. To access the risk of mucormycosis in patients with diabetes

Inclusion criteria

i. All the patients who were diagnosed with Mucormycosis and treated with L AMB
ii. All inpatients and patients who were coming to the emergency department for the liposomal amphotericin B administration
iii. All age groups irrespective of their gender

Exclusion criteria

i. Patients who were not treated with liposomal amphotericin B
ii. Patients who are on other anti-fungals
iii. Patients who were tested negative for mucormycosis
iv. Patients who have undergone only surgical treatment

Data collection method

The data of 40 patients from IPD records were reviewed for the following parameters: Demographic data, comorbidity status, potassium levels and creatinine levels.

All the records were recorded by using structured schedule and entered in Microsoft excel sheet.

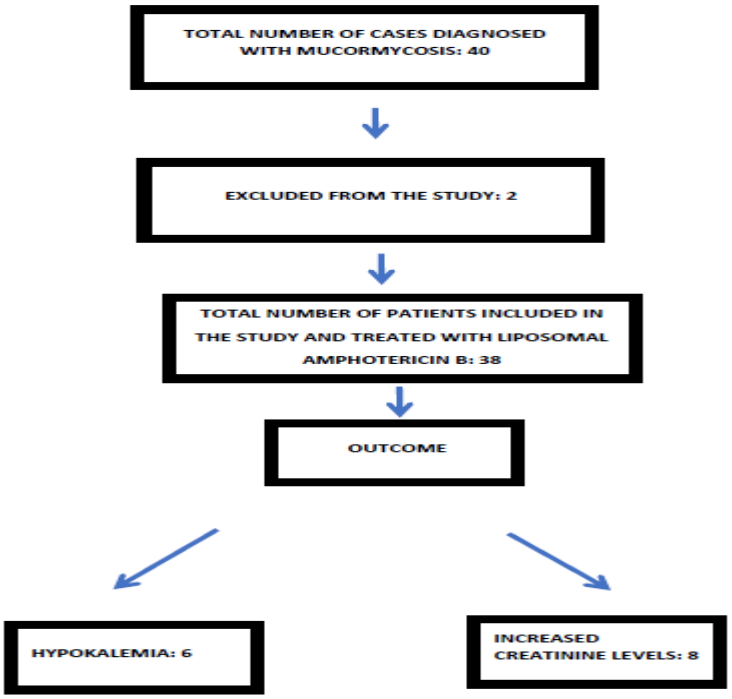
Ethical approval

The study has been approved by the Ethics committee at Continental Hospitals. The study was carried out in accordance with the ethical standards of the committee.

Statistical analysis

Data of the present study was recorded/fed into the computers and after its proper validation, checked for error, it was compiled and analysed. Findings and patterns have been noticed and presented in the form of pie charts, tables and bar graphs.

Flow chart



RESULT

A total of 40 patients were identified, with two testing negatives for mucormycosis and the remaining 38 testing positive and being treated with a combination of liposomal amphotericinB and potassium supplements.

1. Patient Characteristics and Predisposing factors

The age of the patients ranged from 3-70 years with a median age of 47.5 years. The male to female ratio of patient who were on liposomal amphotericin b was 8.5:1. Out of 40 patients twenty-one patients (55%) were a known case of diabetes. All patients had a history of COVID- 19 infection among which 21 patients were on steroids whereas 17 patients didn't have a properhistory of steroid treatment. From the total number of patients 32 patients survived mucormycosis who were treated with the liposomal amphotericin b, while six expired of severe mucormycosis despite of treating with L-AMB. Continuous monitoring of potassium and creatinine levels of the patients were done during the course of the treatment.

Laboratory values in the form of biochemistry results were collected from electronic medical charts. Data (Including the age, serum creatinine levels, potassium levels of the patients) were presented as the mean standard deviation. The grade of the hypokalemia was assessed.

2. Investigation of the factors affecting potassium supplementation during L-AMBadministration

The change in the serum potassium levels during the L-AMB administration is shown in Fig 4, divided into 3 categories. In the laboratory reports collected after 3 days of administration of L-AMB, the serum potassium levels significantly decreased when comparing the levels prior to the initial L-AMB administration. Subsequently, the levels significantly increased following the potassium supplementation in majority of cases. By the end of treatment levels recovered in majority of the patients. A significant difference was identified when compared with the initial and final values of potassium during the L-AMB administration.

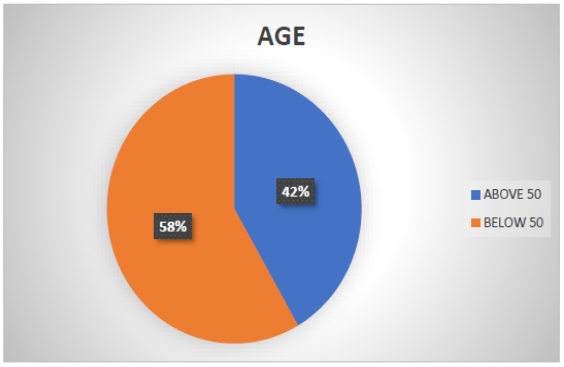


Fig. No. 1

The above pie chart (Fig No 1) represents the comparison between the proportion of patients within the age group above 50 years and below 50 years. Among the total number of patients, 58% of the patients who were diagnosed with mucormycosis were below the age of 50 years whereas only 42% of the patients were above the age of 50.

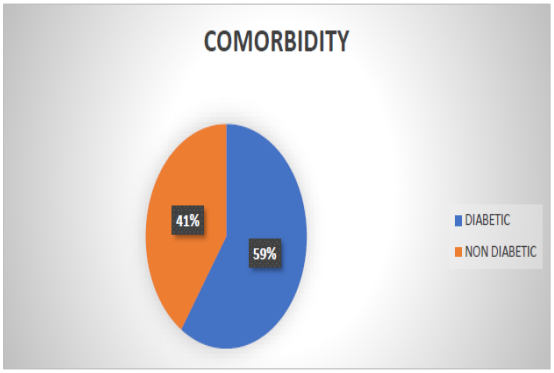


Fig. No. 2

The above pie chart (Fig No 2) provides information about the patients co-morbid status. According to the data among 38 patients majority mucormycosis of them was a known case of diabetes (55%) compared to the patients without diabetes (45%).

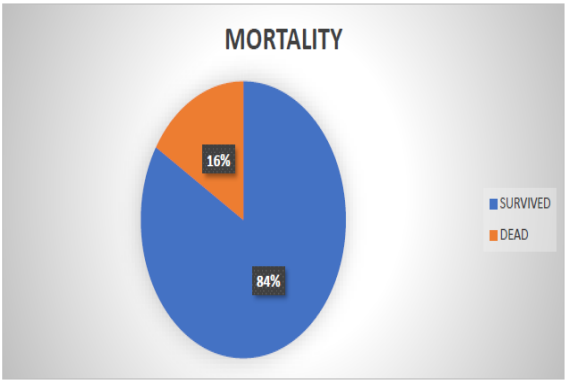


Fig. No. 3

The above pie chart (Fig No.3) illustrates mortality rates of the patients who were presented with mucormycosis. Overall it could be seen that 84% of patients survived whereas 16% deathshave been reported.

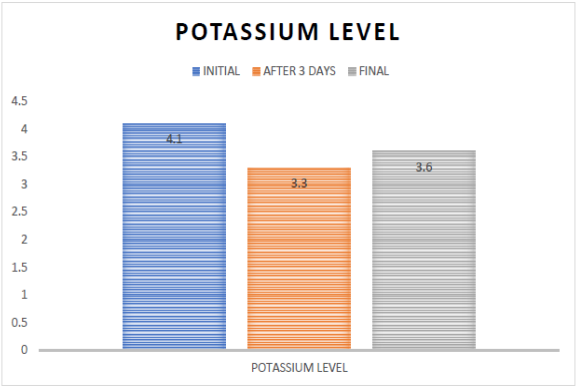


Fig. No. 4

The bar chart illustrate (Fig No. 4) fluctuations in the potassium levels of the patients who were on mucormycosis treatment. It is clear that at the beginning of the treatment the potassium levels of the patients were on normal range (4.1mmol/L) and as the treatment proceeds there was an average drop (3.3mmol/L) in the potassium levels of the patients. By the end of the treatment the average potassium levels of the patients were found to be 3.6mmol/L.

Out of 38 patients 5 were reported with low potassium levels at the time of admission as they were already on liposomal amphotericin B treatment, whereas the other 33 patients were reported with normal potassium levels and the potassium levels were repeated on the day-3 of the treatment and found to be dropping in majority of the patients. Out of these 33 patients, 12patients had normal potassium levels, whereas 13 patients potassium values were in the range of k:3.5-3.0 and on the other hand 8 patients potassium levels dropped below 3.0.

Table 1

S. no	Potassium level(mmol/l)		
	Initial	After 3 days	Final
1	4.2	3.2	3.6
2	3.8	2.7	3.6
3	4.1	3.2	4.5
4	3.1	3.4	3.9
5	3.8	2.8	3.4
6	3.7	3.3	3.1
7	5.1	2.6	2.9
8	4.1	3.4	3.5
9	4.3	2.9	3.8
10	5.6	4.4	3.6
11	3.9	3.1	3.1
12	3.8	3.1	3.4
13	5	4.7	4.8
14	4.7	4	3.5
15	4.8	3.8	3.5
16	5.4	3.7	3.7
17	3.6	3.5	2.9
18	3.8	3.1	4.7
19	4.2	3.3	3.5
20	5.5	3.3	4
21	3.5	2.8	3.4
22	4.2	3.3	3.8
23	3.3	3.2	3.9
24	4.2	2.9	4.2
25	5.0	4.1	4.7
26	3.1	3.4	3.9
27	3.9	3.2	2.7
28	3.2	3.3	4.0
29	4.1	3.4	3.6
30	4.1	3.7	3.9
31	4.5	3.7	2.6
32	4.3	4.2	4.6
33	3.1	3.1	3.2
34	3.9	3.2	3.7
35	4.1	2.8	3.4
36	4.6	3.7	2.9
37	4.3	3.7	3.3
38	4.0	2.5	4.3
∑	157.9	127.7	139.1
Av g	4.1	3.3	3.6

In a total of 38 patients who were tested positive for mucormycosis the average initial potassium level was 4.1 among which the least recorded potassium level was 3.1mmol/L. A total of 5 patients were reported with low potassium levels during admission as they were already started on the L-AMB treatment. Laboratory reports

collected after 3 days from the start of L-AMB treatment indicates that 26 patients had a dip in the potassium levels compared to initial levels among which the least reported was 2.5mmol/L. Potassium supplements either intravenous or oral route were administered as a measure of hypokalemia correction. Amphotericin predictably depletes potassium and magnesium.[14,26] Thus, scheduled supplementation only without additional measurement or replacement doses would be feasible. Although there is some risk of hyperkalemia due to replacement, the predictable nature of electrolyte wasting allows for scheduled replacement without significant fear of hyperkalemia.

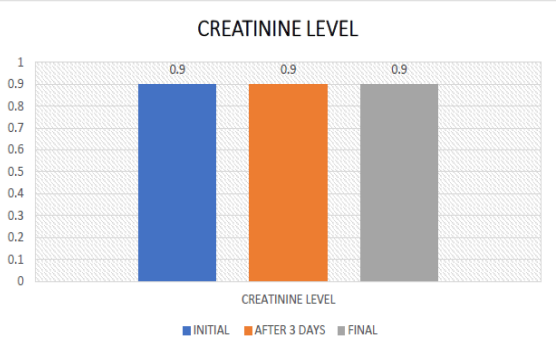


Fig. No. 5

The above bar graph (Fig No 5) illustrates average creatinine level of patients who were on liposomal amphotericin b treatment for mucormycosis, divided into three differentcategories (initially level, level after 3 days of starting the treatment and final level). Overall, itcould be seen that there is mere increase in the creatinine levels after 3 days of liposomal amphotericin b treatment whereas the initial and final levels remains the same.

S no.	Creatinine level(mg/dl)		
	Initial	After 3 days	Final
1	0.5	1.3	1.3
2	0.66	1.3	0.6
3	0.6	0.8	0.7
4	1.3	0.9	1
5	0.8	1.2	0.7
6	1.5	1.0	1
7	0.7	1.1	1
8	0.5	0.6	0.5
9	1.8	1.7	1.6
10	3	2.3	1.2
11	1.8	2	1.1
12	0.7	0.8	0.8
13	1.3	1.2	1.8
14	1	1.4	1.4
15	0.8	0.8	0.8
16	0.7	0.9	1
17	0.9	0.1	0.7
18	1.2	1.8	1.7
19	0.6	0.7	0.7
20	1.3	1	2.5
21	0.6	0.7	0.7
22	0.6	0.5	0.7
23	1.7	1.3	0.8
24	1.4	2.2	1.2
25	1.1	1.3	1.0
26	1.3	0.9	1
27	0.3	0.4	0.3
28	0.6	0.7	0.6
29	2.0	0.7	1.3
30	0.6	0.5	0.7

31	0.8	0.5	0.8
32	0.7	0.5	0.6
33	1.0	1.4	1.1
34	0.6	0.9	1.3
35	1	0.7	1
36	0.4	0.4	0.3
37	1	1.2	1.2
38	0.4	0.5	0.6
∑	37.76	38.2	37.3
Avg	0.9	1	0.9
% Increa se in creati nine level	11(28.94%)	11(28.94%)	8(21.05%)

Out of 38 patients 11 were reported with high creatinine levels intially during the admission. The highest reported initial creatinine level was 2 mg/dl. Laboratory reports after 3 days of start of L-AMB suggest 11(28.94%) patients had a hike in the creatinine level among which the highest was 2.3 mg/dl. By the end of the treatment with L-AMB, 8(21.05%) patients were still reported to have a higher creatinine level whereas the rest were on a normal range of creatinine. There is no significant difference in the creatinine clearance values.

DISCUSSION

Rhinocerebral mucormycosis is a common clinical form of mucormycosis. The invasive natureof the pathogen, the proximity of the infectious process to the orbit and intracranial structuresand immunodeficiency of the host, all combine to make this entity a debilitating and often lethal disease.[8]

Mucormycosis is an aggressive opportunistic infection due to fungi of the Mucoraceae family,which includes the genera Rhizopus, Mucor and Absidia.[1]

There is a possibility of a correlation between COVID-19 and mucormycosis infections. Administration of steroids results in a neutrophilic leukocytosis and the impaired ability of leukocytes to migrate to the site of inflammation due to its inhibitory effects on cytokines and chemokines. Steroids are also known to cause lymphopenia (T more than B cells). Prolonged use of glucocorticoids is known to increase the risk of the patient to infections especially many opportunistic ones. In a case report published by Mehta et al where they have reported a case of post COVID-19 rhino-orbital mucormycosis in which the patient received steroids according to the protocols after which he developed mucormycosis.[9]

Age and Gender

According to our study majority of the patients diagnosed with mucormycosis were below 50 years of age group when compared to above 50 years of age. In our study majority of the patients were around the age of 25-70 years and there were only two pediatrics who were 3 and 7 years of age. A study shown that None of the patient below 30 years of age has developed mucormycosis post Covid-19 infection. It can be attributed to their immunity and less incidence of comorbidity in young adults.[10]

According to other studies majority of the age group was above 40 years.[10–13]

Unlike other studies our study also says that male population was majorly affected rather thanfemales.[11,12]

whereas few studies shown that females ratio was slightly higher than males[13]

To asses the risk of mucormycosis in patients with diabetes

As per our study the ratio of patients presented with diabetes were alarmingly high contributingto 56% of our sample size when compared to non diabetic patients which were 44%. Most of studies have also concluded that diabetic patients were more prone to mucormycosis than non-diabetic patients.[10,14]

Mortality

Of the total number of patients, six patients (16%) died, of them majority of the patients had ahistory of diabetes.

Amphotericin B

A comprehensive systemic review and meta-analysis of case reports of mucormycosis by Jeong *et al*. concluded amphotericin to be the mainstay antifungal agent for pharmacotherapy of mucormycosis.[2]

The median treatment dosage for these infections was 4 mg/kg per day (range, 1–15 mg/kg per day). Favorable response and survival rates were both 51%. In 44 patients who received liposomal amphotericin B as first-line therapy, the response rate was 61%.[16] Our study also favors the survival of patients on l amp b with minimal side effects where our survival rate is 84% of total sample.

Amphotericin B induced Hypokalemia and Nephrotoxicity

Of all the patients 68% of patients had a drop in potassium levels on third day of treatment with liposomal amphotericin b. In most of the studies they have also concluded that there is significant dip in potassium levels after initiation of liposomal amphotericin B

treatment.[2,17,18]

In our study population it was found that there were very minimal fluctuations of serum creatinine during the course of the treatment with liposomal amphotericin B.

Since the introduction of (Conventional) amphotericin B as treatment of fungal infections, nephrotoxicity has been a major concern. Nevertheless, nephrotoxicity has significantly decreased after the introduction of the liposomal formulation of amphotericin B. A decrease in dosage could also be beneficial in mitigating the drug-related renal toxicity. However, nephrotoxicity occurring at the end of the anticipated therapy period has been a reason to stop antifungal treatment prematurely and instead evaluate the natural course of the disease.

Importantly, the associated nephrotoxicity was reversible in the majority of cases after cessation of therapy or dose alteration.[19]

The data demonstrate similar response rates for a 3-mg/kg daily regimen, compared with a high-dose regimen of 10 mg/kg per day for the first 14 days of treatment, for both overall response and survival.[16]

Both clinical and observational studies have suggested an early "window" of 10 to 14 days when nephrotoxicity risk is lowest with L-AMB, which may be shortened in patients receiving concomitant nephrotoxic agents or aggressive diuresis.[20]

CONCLUSION

In this study majority of the patients had drop in potassium levels but no major fluctuations were observed in creatinine levels. Mucormycosis patients on Liposomal Amphotericin B needs careful monitoring of electrolytes notably potassium, these abnormalities can be prevented by early administration of potassium supplements.

REFERENCES

1. Fisher EW, Toma A, Fisher PH, Cheesman AD. Rhinocerebral mucormycosis: Use of liposomal amphotericin B. J Laryngol Otol, 1991; 29, 105(7): 575–7.
2. Kajal S, Naeem S, Gupta P, Kairo A, Ahmed A, Verma P, et al. Sinonasal mucormycosis and liposomal amphotericin B: A quest for dose optimization. Indian J Pharmacol [Internet], 2022; 1 [2022, 22], 54(2): 90. Available from: https://www.ijp- online.com/article.asp?issn=0253-7613;year=2022;volume=54;issue=2;spage=90;epage=96;aulast=Kajal
3. Prakash H, Chakrabarti A. Epidemiology of Mucormycosis in India. Microorganisms, 2021; 4, 9(3): 523.
4. USAMI E, KIMURA M, KANEMATSU T, YOSHIDA S, MORI T, NAKASHIMA K, et al. Evaluation of hypokalemia and potassium supplementation during administration of liposomal-amphotericin B. Exp Ther Med, 2014; 7(4): 941–6.
5. Clinical management and monitoring during antifungal therapy for cryptococcal meningoencephalitis in persons with HIV - UpToDate [Internet], 2022; 19. Available from: https://www.uptodate.com/contents/clinical-management-and-monitoring- during-antifungal-therapy-for-cryptococcal-meningoencephalitis-in-persons-with-hiv
6. Stone NRH, Bicanic T, Salim R, Hope W. Liposomal Amphotericin B (AmBisome®): A Review of the Pharmacokinetics, Pharmacodynamics, Clinical Experience and Future Directions. Drugs, 2016; 27, 76(4): 485–500.
7. Ota Y, Obata Y, Takazono T, Tashiro M, Wakamura T, Takahashi A, et al. Association between potassium supplementation and the occurrence of acute kidney injury in patients with hypokalemia administered liposomal amphotericin B: a nationwide observational study. BMC Nephrol, 2021; 30, 22(1): 240.
8. Handzel O, Landau Z, Halperin D. Liposomal amphotericin B treatment for rhinocerebral mucormycosis: how much is enough? Rhinology, 2003; 41(3): 184–6.
9. Mishra N, Mutya VSS, Thomas A, Rai G, Reddy B, M. AA, et al. A case series of invasive mucormycosis in patients with COVID-19 infection. International Journal of Otorhinolaryngology and Head and Neck Surgery, 2021 Apr 23; 7(5): 867.
10. Desai EJ, Pandya A, Upadhya I, Patel T, Banerjee S, Jain V. Epidemiology, Clinical Features and Management of Rhino Orbital Mucormycosis in Post COVID 19 Patients. Indian Journal of Otolaryngology and Head & Neck Surgery, 2022; 15, 74(1): 103–7.
11. Priya P, Rajendran T, Geni V. Mucormycosis in a Tertiary Care Center in South India: A 4- Year Experience. Indian Journal of Critical Care Medicine, 2020; 1, 24(3): 168–71.
12. Nucci M, Engelhardt M, Hamed K. Mucormycosis in South America: A review of 143 reported cases. Mycoses, 2019; 11, 62(9): 730–8.
13. Dolatabadi S, Ahmadi B, Rezaei-Matehkolaei A, Zarrinfar H, Skiada A, Mirhendi H, et al. Mucormycosis in Iran: A six-year retrospective experience. J Mycol Med, 2018; 28(2): 269–73.
14. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. Journal of Fungi, 2019; 21, 5(1): 26.
15. Spellberg B, Kontoyiannis DP, Fredricks D, Morris MI, Perfect JR, Chin-Hong P v., et al. Risk factors for mortality in patients with mucormycosis. Med Mycol, 2012; 50(6): 611–8.
16. Comely OA, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: A randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad Trial). Clinical Infectious Diseases

[Internet], 2007; 15 [2022, 23]; 44(10): 1289–97. Available from: https://academic.oup.com/cid/article/44/10/1289/355162

17. View of Amphotericin B induced hypokalemia in a diabetic patient with rhino-orbitocerebral mucormycosis [Internet], 2022; 23. Available from: https://www.apicareonline.com/index.php/APIC/article/view/144/139
18. Gupta N, Srinivas S, Harikumar A, Devaraja K, Nallapati VT, Saravu K. Deoxycholate amphotericin for management of mucormycosis: a retrospective cohort study from SouthIndia. Infez Med, 2022; (3): 432–9.
19. van de Peppel RJ, Schauwvlieghe A, van Daele R, Spriet I, van't Wout JW, Brüggemann RJ, et al. Outpatient parenteral antifungal therapy (OPAT) for invasive fungal infections with intermittent dosing of liposomal amphotericin B. Med Mycol [Internet], 2020, 1 [2022, 23]; 58(7): 874. Available from: /pmc/articles/PMC7527269/
20. Mrig S, Sardana K, Arora P, Narula V, Arora S, Kapoor A, et al. Adjunctive Use of Saturated Solution of Potassium Iodide (SSKI) With Liposomal Amphotericin B (L-AMB) in Mucormycosis Achieves Favorable Response, Shortened Dose and Duration of Amphotericin: A Retrospective Study From a COVID- 19 Tertiary Care Center. SSRN Electronic Journal, 2021.