USAGE EVALUATION OF NON-CONVENTIONAL AMPHOTERICIN B IN RIYADH ARMED FORCES HOSPITAL

_____Gamal A.EL.Azab,Tawfeeq.EL.Nagar,and Suliman El.Ghorier. _____

The frequency of invasive fungal infections has increased substantially during the last 2 to 3 decades. Patients at risk are those who are immuncompromised as a result of intensive chemotherapy, immunosuppressive therapy or HIV infections, and patients in intensive care units.[1]

The drug of choice since the early 1950s has been amphotericin B, which is poorly water soluble polyene which binds to membrane sterols of both fungal and human cells.[2] It has a broad spectrum of antifungal activity, with minimal development of resistance.[1]

Unfortunately, amphotericin B has a high toxicity profile, including several infusion-related adverse affects (e.g., fever, chills, hypotension), electrolyte wasting, anemia, and dose limiting nephrotoxicity.

Maintaing the efficacy of amphotericin B while minimizing its toxicity has long been the focus of pharmaceutical research. Incorporation of amphotericin B into a liposomal formulation more than 10 years ago was the first attempt to increase its therapeutic index and enhance its clinical value.[3]

Amphotericin B directly damages renal tubules and, as a result of electrolyte wasting, disrupt the tubuloglomerular feedback mechanism. The clinical manifestations of amphotericin B-induced renal damages include azotemia, renal tubular acidosis, hypokalemia, and hypomagnesemia.

Fortunately, preventative therapies such as sodium loading, and the recent Food and Drug Administration (FDA) approval of lipid based amphotericin B products have helped minimize amphotericin B nephrotoxicity.[4]

Amphotericin B lipid complex (Abelcet)® is the first lipid based formulation of amphotericin B approved in November 1995 for treatment of patients with invasive aspergillosis who are refractory to or intolerant of conventional amphotericin B therapy, the indication has now expanded to include all fungal infections. Amphotericin B colloidal dispersion (Amphotec)® approved one year following the amphotericin B lipid complex, and is approved for the treatment of invasive aspergillosis in patients who are either intolerant of or refractory to conventional amphotericin B. a recent supplemental new drug application for empirical therapy in febrile neutropenia, based on double-blinded comparison with amphotericin B, did not receive FDA approval because of insufficient efficacy data. Liposoaml amphotericin B (Ambisome)® received FDA approval in August 1997 for the treatment of patients with aspergillar, candidal, and/or cryptococcal infections refractory to amphotericin B. an additional approved indication is for the empirical treatment of febrile neutropenia.[5]

The exact mechanism(s) by which lipid-based amphotericin B reduces nephrotoxicity is unknown. Five potential mechanisms have been postulated one theory suggests that after systemic administration, the lipid-based amphotericin B taken up by macrophages, which are usually present at the fungal infection site. The macrophages liberate the amphotericin B from the lipid encasing, and release it preferentially at the site of infection, thus preventing systemic amphotericin B exposure. A second theory suggests that

the amphotericin B encapsulated liposomes have a stronger affinity for fungal ergosterol, and hence, is more likely to translocate at fungal cells. Studies have demonstrated that a lipid-based amphotericin B preparations remained intact until it attached to a fungal cell membrane. Third , in vitro data have suggested that lipid-based amphotericin B products do not stimulate the release of the toxic cytokines TNF-α and interleukin-1, which is associated with standard amphotericin B preparations. Other investigator have theorized that fungal cells produce extracellular phospholipases that hydrolyze the lipid encasing, thus releasing amphotericin B at the site of fungal infection. Finally amphotericin B that is bound to high-density lipoprotein cholesterol (HDL-C) may be less nephrotoxic compared with unbound drug or that bind to low-density lipoprotein cholesterol (LDL-C) because there are relatively few HDL-C receptors in the kidney. [12]

The lipid based formulations of amphotericin B are more expensive than the conventional amphotericin B. The cost is $38.55 for 50mg vial of conventional amphotericin B, $188.4 for 50mg vial of liposomal amphotericin B, $194 for 100mg vial of amphotericin B lipid complex, and $160 for 100mg vial of amphotericin B colloidal dispersion.[6]

Strict guidelines for these formulations are so important to avoid inappropriate use and to lessen the acquisition cost.

So the aims of this study are to review the guidelines established for the use these formulations from several literatures, medical centers and infectious diseases societies guidelines, then to evaluate the use of these formulations at Riyadh Armed Forces Hospital.

Priority for selecting drug products for drug utilization evaluation (DUE) are given to products that have recently marketed, those that are frequently prescribed, those that have high potential risk associated with their use, and those that are expensive.[7]

METHODS

In the beginning pilot study has performed, depending on the data from the inventory control the average monthly use (AMU) of liposomal amphotericin B at May 2001 was 235 vials/month, the approximate cost of these vials is about SR188,000 ($50,133).

The high utilization of the this drug is due to the absence of criteria for use of these formulations

The hospital newly have introduced another formulation which is amphotericin B lipid complex (Abelcet)®, so the study include both of two formulation of nonconventional amphotericin B, liposomal amphotericin B and amphotericin B lipid complex.

The guidelines for the use of non-conventional amphotericin B, have been reviewed from several literatures, medical centers, and infectious diseases societies guidelines.

The guidelines that have been followed in the study are:

All non-conventional amphotericin B should be used in:

1) Systemic mycoses, primarily invasive aspergillosis, in patient who are intolerant of

or refractory to conventional amphotericin B, defined as follows:

- Development of renal Dysfunction (serum Cr. Increased to 2.5mg/dl). (should not be used in patient with irreversible renal impairment, dialysis-dependent renal failure) in whom a lack of response with conventional has not been documented.
- Sever or persistent infusion related to adverse reactions, despite premedications or comedication regimens.
- Disease progression after more than or equal to 500mg total cumulative dose of conventional amphotericin B.

2) Leishmaniasis can be treated with *stibogluconate sodium* (IV or IM).
As alternative therapy *Pentamidine isethionate (Pentam 300mg)* or *amphotericin B*
(for visceral and mucocutaneous forms).
Stibogluconate sodium combined with α-interferon or liposomal amphotericin B
(for refractory cases).

The study have received approval from the Riyadh Armed Forces Research and Ethical Committee, and from the pharmacy department. Then the computer department have received request including patient names, order start, order stop, and doses of the lipid amphotericin B, this request covers all orders from 1st. Jul.1999 to 1st.Jul.2001.
The patients have been selected randomly in blocks of two, then the patients case notes have been ordered from the medical records department according to the previous random selection.
Data collection for this DUE have started at Jun./2001 to Dec.2001, and conducted in 64 patients retrospectively, the data were entered along with surveillance reports into a computerized statistical package (SPSS 10 version) for analysis.
Pharmacy department computer system have been used to ensure the results related to the medications, and biochemistry results. The microbiology results have been confirmed with microbiology department (mycology section), to ensure the type of fungal infections that were not found in some of the medical records.
The points of investigation include patient name, age, gender, ward, major clinical presentation, type of non-conventional amphotericin B have been used and doses, is conventional amphotericin B have been used before the lipid based amphotericin B, concurrent drugs that may affect the renal function, creatinine levels before the use of lipid based amphotericin B, is patient on dialysis, type of dialysis, are there adverse reactions with conventional amphotericin B, type of fungal infection,type of fungal invasion, how fungal infections have been approved, is patient neutropenic, and the reason for use of lipid based amphotericin B.

RESULTS

Patients characteristics through the study are 39 male patients and 25 female patients, the study include all patients ages but the majority are adults patients about45%, 25% pediatrics, 17% newborn, and about 13% elderly patients.

About 41% of patients were hematology patients, these cases were not only at (BMU) but also include the adults and pediatrics intensive care units at Riyadh Armed Forces Hospital and Prince Sultan Cardiac Center.
The nephrology patients in the study were about 17% of patients, the remaining patients are at general surgery and other medicine specialties (figure-1).

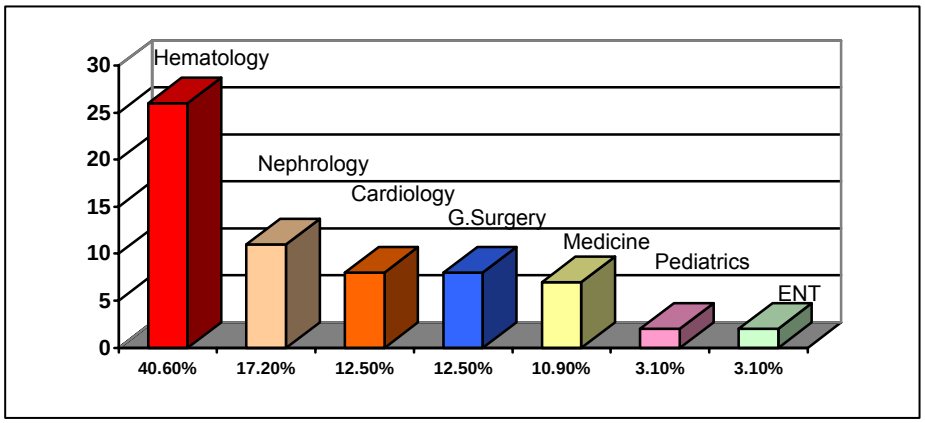


Fig-1: Distribution of lipid based amphotericin B utilization.

Candida albicans affect 42% of patients in this DUE, followed by 23% of *Candida non-albicans*, aspergillus was the third cause of fungal infections of about 16%, 9% was suspected fungal infections, and 5% caused by mucorales species (figure-2).

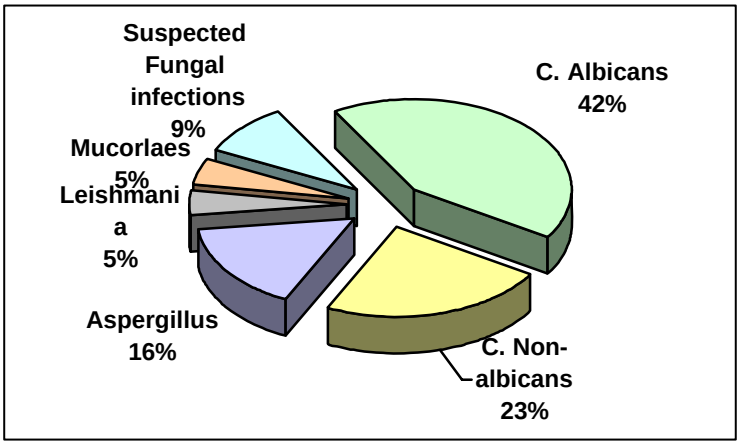


Fig-2: Type of fungal infections.

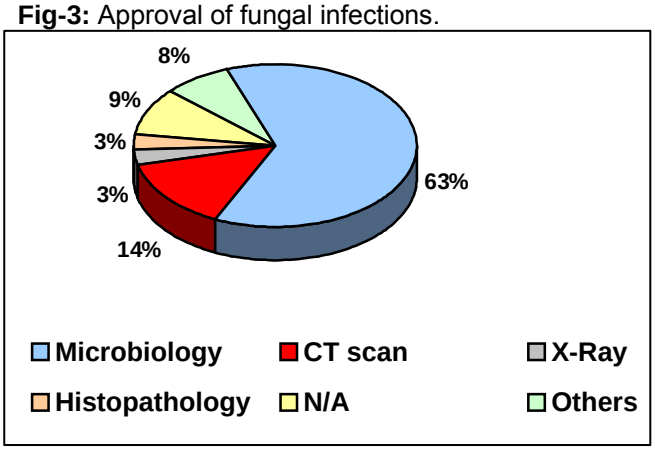
The organ invasions of the fungi are 26% candidemia, 17% disseminated candidiasis, 17% mucocutaneous candidiasis, 16% aspergillosis, and other organ invasions were mucormycosis, candidiuria, and leshmaniasis (non-fungal infections) as shown in (table-1).

Type of Fungal Invasions	% Patients
Candidemia	26%
Disseminated candidiasis	17%
Mucocutaneous candidiasis	17%
Aspergillosis	16%
Mucormycosis	9%
Candidiuria	5%
Leshmaniasis (non-fungal infection)	5%
N/A	5%

Table-1 Prevalence of organ invasion by fungi and leshnania.

Most of the fungal infections among DUE study have been approved by positive cultures by microbiology (63%), followed by CT-scan (14%), and other results are shown in figure-3.

Fig-3: Approval of fungal infections.



According to the guidelines the conventional amphotericin B should started as a first line therapy except if there are contraindication for its use like nephrotoxicity, in this study 52% of patients have received conventional amphotericin B before as a first line therapy, and 48% started immediately on lipid based amphotericin B.

In the 52% of the patients who received the conventional amphotericin B as a first line therapy only 14% of those patients have received total cumulative dose of 500mg or more, where as 38% of patients they received cumulative doses less than 500mg (figure-4). The reasons that the patients did not receive the cumulative dose of 500mg are 2 of the patients have developed adverse reactions to the conventional amphotericin B, and many other patients because of increment of creatinine, and others with unknown reason.

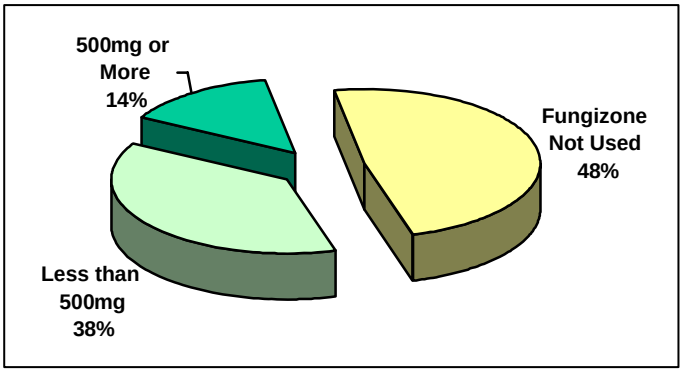


Fig-4: Ranges of conventional amph.B cumulative doses.

Renal function of patients according to creatinine levels was 27% (17) with very high creatinine level and they were on dialysis, 34% (22) have high creatinine levels, and 39% (25) they have normal renal function.

65.6% of patients they received concurrent drugs that may affect renal function together with conventional amphotericin B, these nephrotoxic drugs that have been taken were (23.4% vancomycin), (22% aminoglycosides), and (20.3% cyclosporine).

The total patients who they are on dialysis was 17 patients, 13 of them they are on hemodialysis, 2 on peritoneal dialysis, and 2 they are on prisma. According to the guidelines patient who have irreversible renal function and dialysis dependent should not receive lipid based amphotericin B.
There are 13 patients with irreversible renal function and they are dialysis dependent (hemodialysis) 9 patients received lipid based amphotericin B (figure-5).

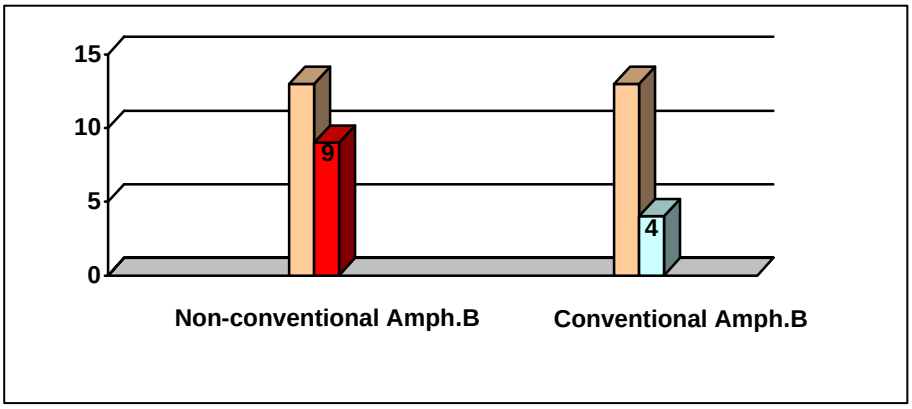


Fig-5: Usage of non-conventional amphotericin B and conventional in patients with irreversible renal impairment and dialysis dependent.

83% of patients have received liposomal amphotericin B (AmBisome)®, and 17% amphotericin B lipid complex (Abelcet)®, this is because the amphotericin B lipid complex have been lately introduced to the hospital formulary.

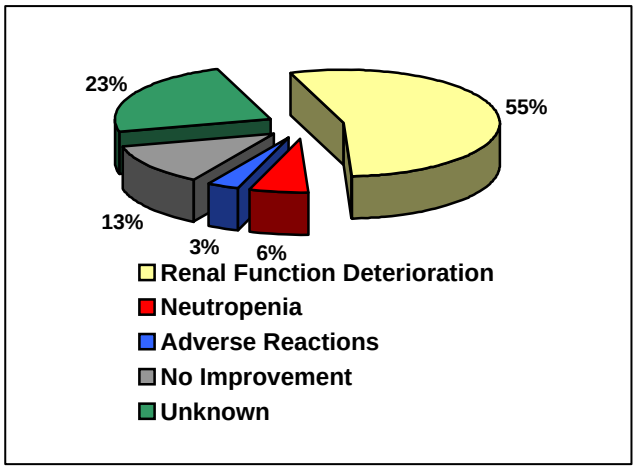


Fig-6: Reasons for use of lipid based amph.B.

The reasons for use of lipid based amphotericib B (figure-6) is the net result of the previous collected data.
The majority of patients were having the non-conventional amphotericin B due to the deterioation of renal function 55%, this deterioration including dialysis dependent patients who they have end stage renal disease, and only patients with elevated ciriatinine levels. It should be noted that 65.6% of patients they are receiving concurrent nephrotoxic drugs that may also affect their renal function.

23% of patients they have no specific reason for their use of non-conventional amphotericin B, i.e., the utilization of lipid based amphotericin B with those patients did not met any of the guidelines mentioned in the method section

13% they have received the lipid form of amphotericin B because of their treatment failure with non-conventional amphotericin B defined by no improvement in temperature, sterilization of cultures, decrease in white blood cell count after at least 500mg dose of conventional amphotericin B.

In patients with persistent neutropenia for 3 days regardless of using broad spectrum antibiotics, patient can be started on amphotericin B with or without antibiotic change, liposomal amphotericin B can be used also if conventional amphotericin B fail to resolve the neutropenia. The use of liposomal amphotericin B for the neutropenic patients here is about 6%.

The least cause of use of non-conventional amphotericin B is development of infusion related adverse effects like (e.g., fever and chills), this was noted Only in 3% of patients.

Lipid-based amphotericin B have been used with no specific indication in 23% of patients, where as 14% of patients with irreversible renal impairment and they are dialysis dependent. The total 37% is inappropriate use of lipid-based amphotericin B.

DISCUSSION

The exact mechanism of amphotericin B nephrotoxicity is not fully understood, but renal vasoconstriction is known to occur, and it appears that the distal tubule epithelial cells are preferentially damaged. Nephrotoxicity likely develops because amphotericin B binds to the sterols in the renal vasculature and epithelial cells. This binding alters the cellular membrane permeability and may stimulate cytokine release and other biochemical reactions within the tubule, resulting in eventual cellular death.[12]
Preventative therapies such as sodium loading, and recent FDA approved lipid-based amphotericin B products have helped to minimize amphotericin B nephrotoxicity.[14]

Efficacy of low-dose dopamine in preventing amphotericin B nephrotoxicity in bone marrow transplant patients and leukemia patients is evaluated in randomly two assigned groups, the result that there were no significantly different for the two groups [14]. Thus, dopamine offers little in the way of prevention of nephrotoxicity associated with amphotericin B therapy.

At San Carlos Clinical Hospital the utilization of non-conventional amphotericin B have been done through retrospective evaluation showed that there is a high percentage of treatments that do not conform with the recommendations contained in the prescription rules. 54% of treatments studied, a poor selection of amphotericin B was made, in 3.5% the use of amphotericin B was not indicated.[15]

Also at Wake Forest University Baptist Medical Center (WFUBMC), evaluation of amphotericin B lipid complex injection have been evaluated through two-year longitudinal evaluation, LeAnne et al. In 156 patients in the study to determine whether amphotericin B lipid complex (Abelcet)® was being prescribed according to institution-approved guidelines and to characterize the patient population receiving (Abelcet)®. 71 patients (46%) met the established guidelines for use; 85 (54%) did not.

CONCLUSION

During the use of non-conventional amphotericin B, the nephrotoxicity that developed also may be caused by other nephrotoxic drugs used concomitantly with the conventional amphotericin B (e.g., vancomycin, aminoglycosides, cyclosporine, tacrolimus, etc). The majority of patients (66%) were receiving concomitant nephrotoxic drugs, the nephrotoxicity that developed was not ruled out whether it is from amphotericin B or other nephrotoxic drugs.
Reconsidering the use of these nephrotoxic drugs may avoid the discontinuation of conventional amphotericin B and use of lipid-based amphotericin B, and hence more cost effective.

Using of conventional amphotericin B in patients with irreversible renal impairment and dialysis dependent may be more cost effective.

It is important to consider the prescribing guidelines of these types of formulations of lipid-based amphotericin B. Unrestricted use of these

formulations can lead to high waste and increment in the total expenditure of the medications.
The restriction can be through authorizing the prescriping of these formulations to the infectious diseases team, or through the applying of restricted guidelines for prescriping. The clinical pharmacist also have a role in selection of the lipid-based amphotericin B. Pharmacy department can program their computer systems to ensure that utilization of these formulations is compatible to the guidelines.

Also considering many of the drugs for Drug Utilization Evaluation (DUE) is an important step in avoiding waste and saving the cost.

REFERENCES:

1. Jan Tollemar, Olle Ringden. Lipid formulations of amphotericin B. Drug Safety 13 (4): 207-218, 1995.
2. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis 1990; 12: 308-29.
3. LeAnne D. Kennedy, PharmD, Julie F.Connelly, PharmD, BCPS and Kevin M. Kuzma, PharmD. Two-year Longitudinal Evaluation of Amphotericin B Lipid Complex Injection in a Tertiary Medical Center. Hospital Pharmacy, Vol. 36, Number 2, pp 176-181, Feb. 2001.
4. Thomas J. Comstock, Renal Disorders, applied therapeutics 7th. Edition, 29-15.
5. Richard A. Jacobs, and R. Joseph Guglielmo and Wong-beringer. Lipid Formulations of Amphotericin B: Clinical Efficacy and Toxicities. Clinical Infectious Diseases, 1998; 27:603-18.
6. John G. Barteltt, Pocket Book of Infectious Disease Therapy 2000, p.16.
7. Annie Wong-Beringer, Pharm.D, Criteria for use of amphotericin B lipid complex injection in adults and children, Am J Health-Syst Pharm Vol 53 Nov 15 1996, 2751-2752.
8. University of Pittsburgh Medical Center, improved antibiotic utilization initiative amphotericin B lipid complex, usage guidelines, www.cbmi.upmc.edu/clem/amphotericin.html
9. Guidelines from the Infectious Diseases Societies of America, 20 April 2000, www.journals.uchicago.edu/CID/journal/issues/v30n4/990666.text.html
10. Wake Forest University Baptist Medical Center, Lipid-Associated Amphotericin B Products, Practice Guidelines and restriction policy, www.wfubmc.edu/intmed/id/hosp/AbelcetUse.html
11. Guidelines for Liposomal Amphotericin B, Department of Pediatrics Affiliated with the University of Ottawa and the Children's Hospital of Eastern Ontario.
12. Thomas J. Comstock, Renal Disorders, Acute Renal Failure, chapter 29, Applied therapeutics, 7th. Edition.
13. Goodwin SD et al. Pretreatment regimens for adverse events related to infusion of amphotericin B. Clin Infect Dis 1995;20:755.

14. Mary J. Camp et al, Efficacy of Low-Dose Dopamine in preventing Amphotericin B Nephrotoxicity in Bone Marrow Transplant Patients and Leukemia Patients, Antimicrob. Agents Chemother., Vol. 42, No.12., 1998, 3103-6.
15. Utilization of non-conventional amphotericin B in the San Carlos Clinical Hospital, www.msc.es/salud/epidemiologia/resp/200004/anfotericina.htm
16. Alan M. Sugar, MD, Empiric Treatment of Fungal Infections in the Neutropenic Host, Review of the literature and guidelines for use, Arch Intern Med-Vol 150, Nov 1990, 2258-64.